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Proposed Re-evaluation Decision

Tralkoxydim

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Overview

Proposed Re-evaluation Decision for Tralkoxydim

After a re-evaluation of the herbicide tralkoxydim, Health Canada's Pest Management Regulatory Agency (PMRA) under the authority of the *Pest Control Products Act* and Regulations is proposing continued registration for the sale and use of products containing tralkoxydim in Canada.

An evaluation of available scientific information found that products containing tralkoxydim have value in the food and crop industry and do not present unacceptable risks to human health or the environment. As a condition of the continued registration of tralkoxydim use on terrestrial food and feed crops, new risk reduction measures are proposed for inclusion on the labels of all tralkoxydim products, and additional data are not being requested at this time.

The PMRA's pesticide re-evaluation program considers potential risks, as well as the value of pesticide products to ensure they meet modern standards established to protect human health and the environment. Regulatory Directive DIR2001-03, *PMRA Re-evaluation Program*, presents the detail of the re-evaluation activities and program structure. Re-evaluation draws on data from registrants, published scientific reports, information from other regulatory agencies and any other relevant information available.

This proposal affects all end-use products containing tralkoxydim registered in Canada. Once the final re-evaluation decision is made, registrants will be instructed on how to address the new risk-reduction measures.

This Proposed Re-evaluation Decision is a consultation document[1] that summarizes the science evaluation for tralkoxydim and presents the reasons for the proposed re-evaluation decision. It also proposes additional risk-reduction measures to further protect human health and the environment.

The information is presented in two parts. The Overview describes the regulatory process and key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessment of tralkoxydim.

The PMRA will accept written comments on this proposal up to 60 days from the date of publication of this document. Please forward all comments to Publications (please see contact information on the cover page of this document).

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1 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

What Does Health Canada Consider When Making a Re-evaluation Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its conditions or proposed conditions of registration.[2] The Act also requires that products have value[3] when used according to label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies hazard and risk assessment methods as well as policies that are rigorous and modern. These methods consider the unique characteristics of sensitive subpopulations in both humans (for example, children) and organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties present when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

Before making a re-evaluation decision on tralkoxydim, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will then publish a Re-evaluation Decision[4] on tralkoxydim, which will include the decision, the reasons for it, a summary of comments received on the proposed registration decision and the PMRA's response to these comments.

For more details on the information presented in this overview, please refer to the Science Evaluation of this consultation document.

What Is Tralkoxydim?

Tralkoxydim is a selective systemic herbicide. It is registered for postemergent use on terrestrial food and feed crops. Tralkoxydim can be used to control a broad spectrum of weeds. It is applied once per year at a rate of 200 g a.i./ha by ground and aerial equipment.

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2 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

3 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (a) efficacy; (b) effect on host organisms in connection with which it is intended to be used; and (c) health, safety and environmental benefits and social and economic impact".

4 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

Health Considerations

Can Approved Uses of Tralkoxydim Affect Human Health?

Additional risk-reduction measures are required on tralkoxydim labels. Tralkoxydim is unlikely to affect human health when used according to the revised label directions.

Potential exposure to tralkoxydim may occur through the diet (food and water) or when handling and applying the product. When assessing health risks, two key factors are considered: the levels where no health effects occur in animal testing and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing, are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed, when tralkoxydim products are used according to label directions.

Tralkoxydim was of slight to moderate acute toxicity by the oral route of exposure in rats and mice. Tralkoxydim was a mild skin and eye irritant in rabbits while it was not a potential skin sensitizer in guinea pigs. Consequently, the following warning statements should appear on the label of the technical product: "Caution Poison, Skin and Eye Irritant".

In rats, there was evidence of oncogenicity in the form of benign Leydig-cell tumours in males and uterine adenocarcinomas in females. In female hamsters, benign liver tumours, uterine tumours and ovarian tumours were noted. There was no treatment-related increase in the number of tumours in male hamsters. Tralkoxydim was not genotoxic and induced no signs of neurotoxicity. Tralkoxydim was teratogenic at a level that resulted in severe maternal toxicity in both rats and rabbits. The main target of toxicity for all species evaluated was the liver. At higher dose levels, the endocrine organs also appear to be targeted by tralkoxydim. When tralkoxydim was given to pregnant animals, effects on the developing fetus were observed at doses that were toxic to the mother, indicating that the fetus is not more sensitive to tralkoxydim than the adult animal.

The risk assessment protects against these effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Residues in Water and Food

Dietary risks from food and water are not of concern.

Reference doses define levels to which an individual can be exposed over a single day (acute) or lifetime (chronic) and expect no adverse health effects. Generally, dietary exposure from food and water is acceptable if it is less than 100% of the acute reference dose or chronic reference dose (acceptable daily intake). An acceptable daily intake is an estimate of the level of daily exposure to a pesticide residue that, over a lifetime, is believed to have no significant harmful effects.

Human exposure to tralkoxydim was estimated from residues in food and drinking water, including the most highly exposed subpopulation (for example, infants smaller than one year old and children 1–2 years old). This aggregate exposure (i.e. to tralkoxydim from food and drinking water) represents less than 2% of the acute reference dose and less than 1% of the chronic reference dose.

The lifetime cancer risk was 3.2×10^{-7} and is considered acceptable. A lifetime cancer risk that is below 1×10^{-6} is considered acceptable for the general population when exposure occurs through pesticide residues in or on food, and to otherwise unintentionally expose individuals. Further information on how the potential cancer risks from pesticides are assessed can be found in Science Policy Notice SPN2000-01, *A Decision Framework for Risk Assessment and Risk Management in the Pest Management Regulatory Agency*.

The *Pest Control Products Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established through the evaluation of scientific data under the *Pest Control Products Act*. Each MRL value defines the maximum concentration in parts per million (ppm) of a pesticide allowed in/on certain foods. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

MRLs for tralkoxydim are currently specified for wheat and barley or processed foods derived from these foods. Where no specific MRL has been established, a default MRL of 0.1 ppm applies, which means that pesticide residues in a food commodity must not exceed 0.1 ppm. The current MRLs for tralkoxydim can be found in the Science Evaluation of this consultation document.

Risks in Residential and Other Non-Occupational Environments

Non-occupational risks are not of concern.

Tralkoxydim is not registered for use in any residential areas. Therefore, there are no potential residential or other non-occupational risks.

Occupational Risks from Handling Tralkoxydim

Occupational risks are not of concern.

Cancer and non-cancer risk estimates associated with mixing, loading and applying activities for proposed label uses are not of concern and additional personal protective equipment are not required beyond what is currently specified on the label.

Postapplication risks are not of concern to workers.

Cancer and non-cancer risks to workers re-entering areas treated with tralkoxydim are not of concern. The minimum 12-hour restricted-entry interval (REI) is proposed for all uses.

Environmental Considerations

What Happens When Tralkoxydim is introduced Into the Environment?

Tralkoxydim poses a potential risk to terrestrial plants, therefore additional risk-reduction measures need to be observed.

When tralkoxydim is released into the environment some of it finds its way into soil and water. However, the chemical is not expected to persist as it is rapidly broken down by soil microbes and by chemical reaction in water. Based on adsorption data, tralkoxydim and some of its transformation products are mobile and hence can move freely in soil. Soil column leaching experiments however, indicate that the mobility of tralkoxydim through soil is limited. Under field conditions, tralkoxydim is shown to dissipate quickly with no residues detected below 10 cm of soil depth beyond 30 days. Although there is no monitoring data available for tralkoxydim to confirm or refute its presence in groundwater, modeling data indicate that tralkoxydim does not leach to groundwater. Based on laboratory, field and modeling data, tralkoxydim is not expected to pose a risk to groundwater contamination. Water runoff on the soil surface can also move the residues into nearby bodies of water, for example, ponds and rivers. Tralkoxydim has not been detected in surface water; however, Canadian water monitoring data of tralkoxydim is limited. Several tralkoxydim transformation products are expected to be formed in soil and aquatic systems. The major transformation products of tralkoxydim are not expected to be a concern to terrestrial and aquatic life.

Tralkoxydim is not expected to pose a risk to wild birds and mammals, bees, other arthropods, fish, amphibians, invertebrates, aquatic plants and algae. However, tralkoxydim does present a risk to sensitive terrestrial plant species that may be exposed to the chemical as a result of spray drifting. To reduce the effects of tralkoxydim in the environment, buffer zones and precautionary label statements are required.

Value Considerations

What is the Value of Tralkoxydim?

Tralkoxydim controls a broad spectrum of grassy weeds in major cereal crops.

In Canada, tralkoxydim has been one of the widely used herbicides (Group 1 graminicide) in cereal crop production since it was first registered in 1992. It is the only graminicide registered for use in perennial cereal rye in the year of crop establishment and in cereals underseeded to forage legumes such as alfafa, birdsfoot trefoil, sainfoin and clovers. Tralkoxydim can be tank-mixed with several broadleaf herbicides to broaden the spectrum of weed control. In addition, it can also be tank-mixed with insecticides for one pass weed and insect control. Tralkoxydim reduces a portion of the economic losses incurred by weeds estimated at $368 million in the early 1990s for barley, wheat and rye in Canada. Although tralkoxydim plays a role in mitigating resistance development in weeds to other herbicide groups, consideration has to be given to resistance management as three species of grassy weeds have already been reported to be resistant to the widespread and frequent use of this graminicide in Canada.

Measures to Minimize Risk

Labels of registered pesticide product labels include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law. As a result of the re-evaluation of tralkoxydim, the PMRA is proposing further risk-reduction measures for product labels.

Human Health

- Additional label statements to clarify the maximum number of applications per year.
- A restricted-entry interval to protect workers entering treated sites.
- Statements for personal protective equipment are updated and standardized between the product labels.

Environment

- Additional advisory statements to protect non-target terrestrial plants and to reduce the potential for tralkoxydim in runoff to adjacent aquatic habitats.
- Buffer zones for terrestrial habitats.

Next Steps

Before making a re-evaluation decision on tralkoxydim, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will then publish a Re-evaluation Decision, which will include the decision, the reasons for it, a summary of comments received on the proposed decision and the PMRA's response to these comments.

Other Information

When the re-evaluation decision is made, the PMRA will publish an Evaluation Report on Tralkoxydim in the context of this re-evaluation decision (based on the Science Evaluation of this consultation document). In addition, the test data on which the decision is based will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

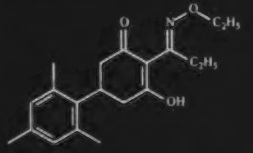
1.0 Introduction

Tralkoxydim is a selective systemic herbicide. It belongs to the cyclohexanedione chemical family and is classified as a Group 1 herbicide. The herbicidal activity of tralkoxydim is due to the inhibition of the plant enzyme acetyl CoA carboxylase (ACCase).

Following the re-evaluation announcement for tralkoxydim, Syngenta Crop Protection Canada Inc., the sole registrant of the technical grade active ingredient and primary data provider in Canada, indicated it would continue to support all uses included on the label of Commercial Class end-use products. There are no Domestic Class end-use products containing tralkoxydim registered in Canada.

2.0 The Technical Grade Active Ingredient, Its Properties and Uses

2.1 Identity of the Technical Grade Active Ingredient

Common name		Tralkoxydim
Function		Herbicide
Chemical Family		Cyclohexanedione
Chemical name		
1	International Union of Pure and Applied Chemistry (IUPAC)	(*RS*)-2-[(*EZ*)-1-(ethoxyimino)propyl]-3-hydroxy-5-mesitylcyclohex-2-en-1-one
2	Chemical Abstracts Service (CAS)	2-[1-(ethoxyimino)propyl]-3-hydroxy-5-(2,4,6 trimethylphenyl)-2-cycohexen-1-one
CAS Registry Number		87820-88-0
Molecular Formula		$C_{20}H_{27}NO_3$
Structural Formula		
Molecular Weight		329.44

Registration Number	Product Name	Guarantee
22413	Tralkoxydim Technical	98.1% NS (limits: 95.35–99.9%)
27596	Tralkoxydim Technical Wet Paste	83.80% NS (limits: 80–88.5%)

Identity of relevant impurities of human health or environmental concern:

Based on the manufacturing process used, impurities of human health or environmental concern as identified in the Canada Gazette, Part II, Volume 142, Number 13, SI/2008-63 (2008-06-25), including TSMP Track 1 substances, are not expected to be present in the product.

2.2 Physical and Chemical Properties of the Technical Grade Active Ingredient

Property	Result	Interpretation
Vapour pressure at 25°C	3.7×10^{-4} mPa	
Ultraviolet (UV)/visible spectrum	λ (nm) — absorption (M^{-1} cm^{-1}) 202 — 55700 240 — 11200 268 — 6690 280 — 7290	Not expected to absorb at λ >300 nm
Solubility in water at 20°C	6 (pH 5), 6.7 (pH 6.5), 9800 (pH 9) (all in mg/L)	
n-Octanol–water partition coefficient at 20°C	log K_{ow} = 2.1	
Dissociation constant	pKa = 4.3 (25°C)	

2.3 Description of Registered Tralkoxydim Uses

Appendix I lists all tralkoxydim products that are registered under the authority of the *Pest Control Products Act*, including two technical grade active ingredients and five Commercial Class end-use products.

Appendix II lists all the uses for which tralkoxydim is presently registered. All uses were supported by the registrant at the time of initiation of re-evaluation and were, therefore, considered in the health and environmental risk assessments. Also presented is whether any of the uses were added through the Pest Management Regulatory Agency (PMRA) Minor Use Program. While currently supported by the registrant, the data supporting these minor uses was originally generated by a user group.

Uses of tralkoxydim belong to the following use-site categories: terrestrial feed crops and terrestrial food crops. The crops specifically include cereal crops (spring wheat, winter wheat, durum wheat, barley, triticale, spring rye and winter rye) grown alone or underseeded to forage legumes (i.e. alfalfa, birdsfoot trefoil, sainfoin and clovers). Tralkoxydim is also registered as a User Requested Minor Use Label Expansion on seedling and established intermediate and crested wheatgrass, creeping red fescue, and meadow and smooth bromegrass grown alone or underseeded to cereals (for seed production purposes only), for establishment of northern wheatgrass, western wheatgrass, slender wheatgrass (for seed production purposes only) and for perennial cereal rye in the year of crop establishment.

3.0 Impact on Human and Animal Health

Toxicology studies in laboratory animals describe potential health effects resulting from various levels of exposure to a chemical and identify dose levels where no effects are observed. Unless there is evidence to the contrary, it is assumed that effects observed in animals are relevant to humans and that humans are more sensitive to effects of a chemical than the most sensitive animal species. The health effects noted here were observed in animals at dose levels at least 100-fold (often much higher) above levels to which humans are normally exposed through use of products containing this chemical.

3.1 Toxicological Summary

A detailed review of the toxicological database for tralkoxydim was conducted. With the exception of a short-term inhalation study, the database for tralkoxydim is complete and consists of the full array of toxicity studies currently required for hazard assessment purposes. The majority of studies were conducted between 1984 and 1991 with a few studies performed in 1994, 1996 and 2002. All of these studies were conducted in accordance with the accepted international testing protocols and Good Laboratory Practices at that time. The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to this chemical pest control product. Throughout the toxicological database, the purity of tralkoxydim ranged from 92.4% to 99.0%. The results of these toxicological studies revealed consistent target organs, no species differences and similar effect levels for the different exposure scenarios. Based on this information, the different purities of tralkoxydim were not expected to impact upon the study conclusions.

Tralkoxydim is a cyclohexanedione herbicide capable of inhibiting acetyl coenzyme A (CoA) carboxylase activity. The acetyl CoA carboxylase enzyme is responsible for catalyzing a two-step condensation of acetyl-CoA with bicarbonate to form malonyl-CoA, the committed step of the fatty acid synthesis pathway. In the first step, the biotinylated enzyme is carboxylated in the presence of bicarbonate and adenosine triphosphate. In the second step, the carboxylated enzyme transfers the carboxyl group to acetyl-CoA to form malonyl-CoA. Inhibition of this process will ultimately lead to a disruption in fatty acid biosynthesis. In plants, the inhibition of acetyl CoA carboxylase will result in the inhibition of acyl lipid biosynthesis, eventually resulting in the death of the plant.

Tralkoxydim was rapidly absorbed in rats after single and repeat oral dosing and demonstrated no potential for bioaccumulation. Tralkoxydim was rapidly excreted in rats, predominantly via the urine and bile with some via the feces. Male rats, compared to females, excreted a higher proportion of the dose in the urine and less in the feces. Biliary cannulated rats excreted approximately 70% of the administered dose in the bile and 10% in the urine indicating significant enterohepatic circulation.

In rats, tralkoxydim was initially metabolized to tralkoxydim alcohol which was further oxidized to the corresponding diol and acid (major metabolite). These three metabolites accounted for almost 90% of the metabolites in bile and urine while the other minor metabolites (alcohol oxazole, acid oxazole, diol oxazole) were identified in trace to small amounts. Repeat dosing did not alter the formation of metabolites. Males demonstrated an increase in the extent of enterohepatic circulation along with urinary excretion of tralkoxydim diol.

Tralkoxydim was rapidly absorbed in hamsters after single oral dosing and demonstrated no potential for bioaccumulation. Tralkoxydim was rapidly excreted in both sexes of hamsters with recoverable residues that were significantly higher in urine than in feces. The metabolic profile in urine was similar for both male and female hamsters. The two major metabolites that were identified were tralkoxydim acid (major metabolite) and tralkoxydim acid oxazole. A human study, intended only to evaluate whether tralkoxydim acid could be used as an indicator of tralkoxydim exposure, also identified tralkoxydim acid as a major metabolite.

Tralkoxydim was of slight to moderate acute toxicity by the oral route of exposure in rats and mice. A supplemental study in rats indicated that tralkoxydim was of low acute toxicity by the dermal route. When administered by the inhalation route, tralkoxydim was of low acute toxicity to rats. Clinical signs associated with acute exposure to tralkoxydim in rats and mice included reduced activity, lacrimation, dehydration, hypothermia, piloerection, depressed respiration, reduced righting reflex and stability shortly after dosing. Tralkoxydim was a mild skin and eye irritant in female rabbits (neither examined males), and was not a potential skin sensitizer in a supplemental study in guinea pigs.

In repeat-dose toxicity studies, the main target of toxicity for all species evaluated (rats, dogs, mice and hamsters) was the liver. At higher dose levels, the endocrine organs also appear to be targeted by tralkoxydim. Clinical chemistry and pathological findings in the rat and dog studies were indicative of hepatotoxicity, along with alterations in hematology that were indicative of anemia. In the rat and dog, disturbances in clotting factors and fat metabolism were also noted. Changes considered to be a general response to tralkoxydim exposure in hamsters included liver enlargement, proliferation of smooth endoplasmic reticulum in hepatocytes, decrease in hepatocyte vacuolation as well as evidence of anemia and changes in lipid metabolism. In three strains of mice, similar organ weight alterations and hepatotoxic effects to the rat and dog were noted. In mice, a yellow/brown pigment, subsequently demonstrated to be N-methyl protoporphyrin IX, was found to accumulate in bile ducts and Kupffer cells.

In dogs, pathological changes were also observed in the testes, epididymides and erythrocytes with an effect on the adrenal gland demonstrated by increased weight and minimal vacuolation of cells in the zona fasiculata and reticularis. A comparison between the 90-day and 12-month studies indicated a time-dependent increase in severity of these effects on the adrenals. Epididymal weights were reduced along with minimal epididymal interstitial lymphoid infiltration in the 90-day study but were not investigated in the 12-month study. In the 12-month study, thyroid weights were increased without any other treatment-related pathology findings.

The tralkoxydim-treated animals (hamsters, rats and dogs) all demonstrated hypolipidaemia (reduced cholesterol and triglyceride levels), induction of hepatic cytochrome P450 and smooth endoplasmic reticulum. The reduced cholesterol levels noted throughout the database may be related to steroid hormonal imbalances which could potentially explain the pathological alterations in the reproductive organs which have been seen in the toxicity studies. The biochemical mode of action in mammals is probably similar to that found in plants, where tralkoxydim has been shown to inhibit acetyl CoA carboxylase, and so disrupts fatty acid biosynthesis.

The development of porphyria in mice only is likely a species-specific response to tralkoxydim, precluding the use of mouse toxicity data in human risk assessment. In three different strains of mice, tralkoxydim has been shown to rapidly and severely inhibit hepatic mitochondrial ferrochelatase activity while increasing hepatic 5-aminolevulinic acid synthetase (ALAS) activity (a rate limiting enzyme in porphyrin synthesis) thus inhibiting heme biosynthesis. Tralkoxydim causes a rapid accumulation of the hepatic enzyme N-methyl protoporphyrin IX (a potent inhibitor of ferrochelatase) which competes with the normal substrate, protoporphyrin IX, for the active site. The enzyme inhibition results in a compensatory overstimulation of heme synthesis and the accumulation of porphyrins in the liver which eventually leads to cholestasis. No significant degree of porphyrin accumulation was noted in rats, hamsters, guinea pigs or marmosets. This finding was supported by in vitro studies in mice, rat and human hepatocytes. Based on the weight of evidence, it appears unlikely that tralkoxydim would cause porphyria in humans.

In a two-year chronic/carcinogenicity study, rats fed diets containing tralkoxydim experienced hepatotoxicity based on alterations in clinical chemistry, increased organ weight and histopathological changes. Hematological, clinical chemistry and pathological findings also indicated anemia and an effect on the kidney. In males, the testes and epididymides were also target organs. Increased incidences of hyperplasia, benign Leydig-cell tumours, granulomas of the testes and reduced numbers of spermatozoa in the lumens accompanied by the presence of an increased number of early, nucleated sperm precursor cells in the epididymides were noted. In females, uterine adenocarcinomas were increased above concurrent and historical controls as was the incidence of bilateral retinal atrophy (earliest lesion noted at week 69). The effect of tralkoxydim on the metabolism of lipids such as cholesterol, a precursor of androgens, estrogen and progestrogen, could be a factor in the increased incidence of testicular and uterine alterations. It was concluded that tralkoxydim was tumorigenic in rats in the presence of systemic toxicity.

Syrian hamsters were selected as the second rodent species for chronic toxicity/carcinogenicity testing due to the species-specific hepatic porphyria found in tralkoxydim treated mice which would have limited the dose range in mice. In an 18-month dietary study, female hamsters were found to have a low survival rate (not inconsistent with survival data from other labs); however, sufficient tissues were available for histopathological assessment. The target organs of toxicity in male hamsters were the liver and the testes, as evidenced by increased organ weights. In females, the adrenal glands and kidneys were targeted by tralkoxydim resulting in decreased organ weights. An increased incidence of benign adrenal gland cortical adenomas was seen in all treated-females; however, these lesions did not progress to malignant lesions. Although this study was deemed acceptable for the assessment of chronic toxicity, there were limitations in assessing the potential carcinogenicity of tralkoxydim due to the high mortality noted in all groups of females.

To address the high mortality in the carcinogenicity study conducted in hamsters, the registrant submitted a second Syrian hamster carcinogenicity study with improved survival. The organs that were targeted by tralkoxydim in males included the liver, kidney and the testes as demonstrated by alterations in organ weights and histopathology (liver only). In tralkoxydim-exposed females, an increase in the weights of the liver, the uterus and the ovaries along with alterations in histopathology were noted. There was no treatment-related increase in the number of tumours in male hamsters. In high-dose females, there was an increase in the number of animals with hepatocellular adenomas compared to the control group. As well, females experienced an increase in the incidence of benign uterine adenomas. There were an increased number of females with benign sex cord stromal tumours of the ovary in the mid- and high-dose groups as compared to the control group. Although these tumours were classified under the category of sex cord stromal tumours according to their embryological tissue of origin, the tissue type (granulosa cell, thecal cell, interstitial cell or a mixture of different types) varied. There was no evidence that tralkoxydim affected the histological appearance of the ovarian tumours, no indication of any pre-neoplastic lesions in the ovary and there was no increase in the malignant component of this tumour type. Based on the presence of a variety of tumours in females, tralkoxydim is considered to be tumourigenic in female hamsters.

There was no evidence of a mutagenic potential of tralkoxydim, in a variety of bacterial and mammalian in vitro and in vivo studies.

In the three-generation rat reproduction study, parental toxicity was observed in the form of reduced body-weight gain and food consumption across all generations. Decreased birth weights were the only treatment-related effect on reproductive performance; however, this was noted at maternally toxic doses. Increased liver weights, decreased total litter weights and decreased pup weight gain, were also present in the offspring at maternally toxic dose levels.

Two teratogenicity studies in the rat revealed severe maternal toxicity in the form of increased mortalities, clinical observations (coat staining, piloerection, hunched posture, urinary incontinence and subdued behaviour), decreased body weight and weight gain along with decreased food consumption. An increased incidence of total litter resorptions and post-implantation losses with a consequent decrease in the mean number of live fetuses (due to

both early and late intrauterine deaths) was noted. In the offspring, developmental toxicity was noted at the mid-dose level based on the presence of reduced ossification in the first cervical vertebrae and the odontoid bone. At the high-dose level an increased incidence of intrauterine deaths decreased mean fetal weight, and delayed ossification were noted in the offspring. Evidence of teratogenicity was noted at the high-dose level in the form of treatment-related defects of the vertebral centra including misshapen vertebral centra and fusion of the sacral vertebral centra as well as additional major abnormalities (cleft lip and palate, bilateral curvature of the radius and ulna, edema).

Rabbits administered tralkoxydim by gavage during gestation experienced an increased incidence of abortions along with decreased body weight and food consumption. At this dose level, the number of post-implantation losses was increased with a corresponding decrease in the mean number of live fetuses. At the maternotoxic dose level, potential teratogenicity in the form of an increased incidence of normal length extra thirteenth ribs was observed along with two rare head malformations.

Results of the acute, short-term and chronic tests conducted on laboratory animals with tralkoxydim technical, along with the toxicology endpoints for use in the human health risk assessment, are summarized in Appendix III.

***Pest Control Products Act* Hazard Consideration**

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects. This factor should take into account completeness of the data with respect to the exposure of, and toxicity to infants and children and potential pre- and post-natal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the exposure of and toxicity to infants and children, extensive data were available for tralkoxydim. Data of high quality were available for tralkoxydim and included two developmental toxicity studies in rats, one developmental toxicity study in rabbits and a multigeneration reproduction study in rats. Throughout the database, the main target of toxicity for all species evaluated was the liver while endocrine organs were targeted at higher dose levels. While endocrine activity can be a trigger for a developmental neurotoxicity study (DNT), no study was available for tralkoxydim. Since the liver is the more sensitive target organ in the rat (the model species for the developmental neurotoxicity study), regulating on hepatotoxicity would be considered protective of any potential hormonally-induced effects. In light of the minimal toxicity seen in the reproduction study, the dose levels selected for a developmental neurotoxicity study likely would be comparable to or possibly higher than those tested in the reproduction study. Even if effects were noted in the offspring in a developmental neurotoxicity study, it is anticipated that the current reference doses would afford sufficient protection to any potential effects. Based on this information and the lack of neurotoxicity in the database, a developmental neurotoxicity study is not required for tralkoxydim.

With respect to potential pre- and post-natal toxicity, a pre-natal developmental toxicity study in rabbits did not indicate quantitative susceptibility of rabbit fetuses to in utero exposure. In rats, one of the prenatal developmental toxicity studies indicated that fetuses manifested a marginal delay in ossification (first cervical vertebrae and the odontoid bone) in the absence of maternal toxicity; however, there was no indication of increased susceptibility in the offspring compared to parental animals in the rat reproductive toxicity study at the dose levels tested. Of more concern was the occurrence of malformations and post-implantation losses in both rat and rabbit fetuses in the developmental studies; however, these malformations and post-implantation losses occurred in the presence of severe maternal toxicity (death, abortion and weight loss) and at high doses. While these endpoints (i.e. malformations and embryofetal lethality) are considered serious, the degree of concern is tempered by the accompanying maternal toxicity. It is recognized that maternal toxicity of such severity could in and of itself, bring about adverse consequences in the young.

3.2 Occupational and Non-Occupational Risk Assessment

Occupational risk is estimated by comparing potential exposures with the most relevant endpoint from toxicology studies to calculate a margin of exposure (MOE). This is compared to a target MOE incorporating uncertainty factors protective of the most sensitive human population. If the calculated MOE is less than the target MOE, it does not necessarily mean that exposure will result in adverse effects, but mitigation measures to reduce risk would be required.

Where evidence of carcinogenicity is identified for the active ingredient, a cancer potency factor (Q_1^*) is generated and used to estimate cancer risk. The product of the expected exposure and the Q_1^* estimates the lifetime cancer risk as a probability. A lifetime cancer risk in the range of 1 in 10^{-5} to 1 in 10^{-6} in worker population groups is generally considered acceptable.

3.2.1 Toxicology Endpoint Selection for Occupational Risk Assessment

Short- and Intermediate-term Dermal and Inhalation Risk Assessment (for worker mixer/loader/applicators (M/L/A), custom worker M/L/A, and re-entry workers)
A repeat-dose dermal study, while available, had not yet been reviewed. A repeat-dose inhalation study was not available. Therefore, the results from the oral studies were considered relevant for the risk assessment for these routes of exposure.

For occupational short-term (1–30 days) and intermediate-term (one month–several months) dermal and inhalation assessments relative to the use pattern, the developmental NOAEL of 3 mg/kg bw/day from both oral (by gavage) developmental toxicity studies in the rat was selected. At the next dosage level of 30 mg/kg bw/day, reduced ossification was noted, in the absence of maternal toxicity. The target MOE selected when using this study is 100 thus accounting for standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. Since the delay in ossification was marginal and not corroborated by the results of the multi-generation reproduction study, no additional factors were applied. The target MOE is protective of the malformations and embryofetal lethality observed at higher dose levels of tralkoxydim.

3.2.2 Cancer Risk Assessment

In the absence of mode of action data to support a threshold approach to the cancer risk assessment, a linear low dose extrapolation approach (Q_1^*) was used for tralkoxydim. Unit risks for tralkoxydim, denoted by Q_1^* (representing the upper 95% confidence limit on the slope of the dose-response curve in the low-dose region), were calculated on the basis of the bioassay data from the two year chronic toxicity/carcinogenicity study in rats and the 80-week carcinogenicity study in hamsters. An adjusted Q_1^* value of 1.08×10^{-2} $(mg/kg\ bw/day)^{-1}$ was derived in male rats based on the increased incidence of benign Leydig-cell tumours from the two year chronic toxicity/carcinogenicity study. No mode of action data has been provided to support an assessment of the Leydig-cell tumours as a threshold response. An adjusted Q_1^* value of 1.19×10^{-3} $(mg/kg\ bw/day)^{-1}$ was calculated from the 80-week carcinogenicity study in Syrian hamsters based on the increased incidence of uterine adenocarcinomas in females. For the cancer risk assessment of tralkoxydim, the more conservative adjusted Q_1^* value of 1.08×10^{-2} $(mg/kg\ bw/day)^{-1}$ from the two-year chronic toxicity/carcinogenicity study in rats was selected.

Dermal Absorption
A dermal absorption value of 30% was chosen for the re-evaluation of tralkoxydim based on the studies submitted to the PMRA.

3.2.3 Occupational Exposure and Risk

Workers can be exposed to tralkoxydim through mixing, loading or applying the pesticide, and when entering a treated site to conduct activities such as scouting and/or irrigating treated crops.

Mixer, Loader and Applicator Exposure and Risk Assessment
There are potential exposures to mixers, loaders, and applicators. The following scenarios were assessed:

- Mixing/loading emulsifiable concentrates;
- Groundboom application to field crops (cereal grains, forage grasses); and
- Aerial application to field crops (cereal grains, forage grasses).

Based on the number of applications, workers applying tralkoxydim would generally have a short- to intermediate term (one month–several months) duration of exposure. The PMRA estimated handler exposure based on the following level of personal protection, which is currently on the product labels and the minimum personal protective equipment (PPE) required for applicators:

- Label/baseline personal protective equipment–long pants, long sleeved shirt and chemical-resistant gloves; cotton coveralls are also required for mixers and loaders. For groundboom application, this scenario does not include gloves, as the data quality was better for non-gloved scenarios than gloved scenarios. Gloves are also not required to be worn inside cockpits for aerial application.

Mixer/loader/applicator exposure estimates are based on the best available data at this time.

A chemical-specific biomonitoring study was submitted to the PMRA; however, since major factors such as the formulation, application rate, and application equipment (i.e. closed cab) used in this study are different than what is currently registered in Canada, the data from this study were not considered appropriate for use in this risk assessment.

No acceptable chemical-specific handler exposure data were submitted for tralkoxydim; therefore, dermal and inhalation exposures were estimated using data from the Pesticide Handlers Exposure Database (PHED), Version 1.1. The Pesticide Handlers Exposure Database is a compilation of generic mixer/loader applicator passive dosimetry data with associated software that facilitates the generation of scenario-specific exposure estimates based on formulation type, application equipment, mix/load systems and level of personal protective equipment.

Occupational cancer risk was calculated assuming 40 years of exposure over a 75 year lifetime. The product of the expected exposure and the Q_1^* estimates the lifetime cancer risk as a probability. A lifetime cancer risk in the range of 1 in 10^{-5} to 1 in 10^{-6} in worker populations is generally considered acceptable.

Occupational non-cancer risk estimates associated with mixing, loading and applying tralkoxydim to cereal grains and forage grasses exceed the target MOE at label PPE, and cancer risks were less than 1×10^{-5}. Therefore, risk to workers handling tralkoxydim was not of concern. Refer to Appendix IV for more information.

Postapplication Worker Exposure and Risk Assessment

The postapplication occupational risk assessment considered exposures to workers entering treated fields of cereal grains and forage crops. Based on the tralkoxydim use pattern, there is potential for short-term (< 30 days) postapplication exposure to tralkoxydim residues for workers.

Default dislodgeable foliar residue (DFR) values and activity specific transfer coefficients (TC) were used to estimate postapplication exposure resulting from contact with treated foliage at various times after application. DFR data include the amount of residue that can be dislodged or transferred from a surface, such as the leaves of a plant. A TC is a factor that relates worker exposure to transferrable residues. TCs are specific to a given crop and activity combination (for example, hand harvesting apples, scouting late season corn) and reflect standard agricultural work clothing worn by adult workers. Postapplication exposure activities include scouting and irrigating.

For workers entering a treated site, restricted-entry intervals (REIs) are calculated to determine the minimum length of time required before people can safely enter after application. An REI is the duration of time that must elapse before residues decline to a level where performance of a specific activity results in exposures above the target MOE (i.e. > 100 for short-term dermal exposure scenarios for tralkoxydim).

As no appropriate chemical-specific DFR studies were submitted to the PMRA, the default peak DFR value of 20% of the application rate was used in the assessment.

All postapplication scenarios had MOEs that were above the target MOE on the day of application and cancer risks that were less than 1×10^{-5}. Therefore risk to postapplication workers is not of concern. Mitigation beyond the minimum 12-hour REI is not required. Refer to Appendix IV for more information.

3.2.4 Non-Occupational Exposure and Risk Assessment

There are no residential uses for tralkoxydim; therefore, a residential risk assessment was not required.

3.3 Dietary Risk Assessment

In a dietary exposure assessment, the PMRA determines how much pesticide residue, including residues in milk and meat may be ingested with the daily diet. The exposure to tralkoxydim from potentially treated imports is also included in the assessment. These dietary assessments are age specific and incorporate the different eating habits of the population, at various stages of life. For example, the assessments take into account differences in children's eating patterns, such as food preferences and the greater consumption of food relative to their body weight when compared to adults. Dietary risk is then determined by the combination of the exposure and the toxicity assessments. High toxicity may not indicate high risk if the exposure is low. Similarly, there may be risk from a pesticide with low toxicity if the exposure is high.

The PMRA considers limiting use of a pesticide when risk exceeds 100% of the reference dose. The PMRA's Science Policy Notice SPN2003-03, *Assessing Exposure from Pesticides, A User's Guide*, presents detailed acute and chronic risk assessments procedures.

Residue estimates used in the dietary risk assessment (DRA) may be conservatively based on the maximum residue limits (MRL) or the field trial data representing the residues that may remain on food after treatment at the maximum label rate. Surveillance data representative of the national food supply may also be used to derive a more accurate estimate of residues that may remain on food when it is purchased. These include the Canadian Food Inspection Agency's National Chemical Residue Monitoring Program and the United States Department of Agriculture Pesticide Data Program (PDP).

Acute and chronic non-cancer and cancer dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™, Version 2.0), which uses updated food consumption data from the United States Department of Agriculture's Continuing Surveys of Food Intakes by Individuals, 1994–1996 and 1998.

For more information on dietary risk estimates or residue chemistry information used in the dietary assessment, see Appendix V and VI.

3.3.1 Determination of Acute Reference Dose

To estimate acute dietary risk (1 day) for females of child-bearing age (13–49 years), an oral (by gavage) developmental toxicity study in the rabbit was selected for risk assessment. A developmental NOAEL of 20 mg/kg bw/day was based on increased post-implantation losses and late intra-uterine deaths, decreased mean number of live fetuses and mean litter weight, the presence of two head malformations in fetuses from different litters (exencephaly and cebocephaly) and an increased incidence of normal length extra thirteenth rib occurring at the next dosage level of 100 mg/kg bw/day. Both the malformations and the post-implantation losses were considered relevant endpoints that could result from an acute exposure. While decreased ossification was noted in the rat developmental toxicity study at a lower LOAEL than the LOAEL for the rabbit developmental toxicity study, this effect was associated with repeat exposure and thus not relevant to the acute reference dose. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. With respect to the *Pest Control Products Act* factor, all of the required studies relevant to assessing risks to infants and children were available for this assessment. While significant pre-natal toxicity was demonstrated, the degree of concern was ameliorated by the demonstration of significant maternal toxicity at the same dose levels. Accordingly, the *Pest Control Products Act* factor was reduced to threefold. Therefore, the composite assessment factor is 300.

ARfD: Females ages 13 to 49 years = $\frac{\text{20 mg/kg bw/day}}{\text{300}}$ = 0.067 mg/kg bw/day

For the remainder of the population, the NOAEL of 20 mg/kg bw/day was selected from the same developmental toxicity study in the rabbit based on maternal toxicity (weight loss detected after 1 day of exposure) noted at the next dosage level of 100 mg/kg bw/day. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. With respect to the *Pest Control Products Act* factor, all of the required studies relevant to assessing risks to infants and children were available for this assessment. Although significant pre-natal toxicity was demonstrated in animals, these effects were considered to be relevant in the establishment of an acute reference dose for females aged 13–19 (above) since the effects resulted from in utero exposure and not from the direct exposure of the young. The overall level of concern for pre- and post-natal toxicity for this population (excluding women of child-bearing age) is low and thus, the *Pest Control Products Act* factor was reduced to onefold.

ARfD: General population (excluding females ages 13 to 49 years)
= $\frac{\text{20 mg/kg bw/day}}{\text{100}}$ = 0.2 mg/kg bw/day

3.3.2 Acute Dietary Exposure and Risk Assessment

Acute dietary risk is calculated considering the highest ingestion of tralkoxydim that would be likely to occur on any one day, using food and drinking water consumption data and the estimated residue values on those commodities. A statistical analysis allows all possible

combinations of consumption and residue levels to be combined to estimate a distribution of the amount of tralkoxydim residue that might be consumed in a day. A value representing the high end (95th percentile) of this distribution is compared to the ARfD, which is the dose at which an individual could be exposed on any given day and expect no adverse health effects. When the expected intake of residues is less than the ARfD, then acute dietary exposure is considered to be acceptable.

The acute potential daily intake of tralkoxydim from food and water accounted for < 2% (95th percentile of exposure) of the ARfD for all subpopulations, and is therefore, not of concern.

3.3.3 Determination of Acceptable Daily Intake

The main target of toxicity for tralkoxydim in all evaluated species (rats, dogs, mice and hamsters), was the liver with signs of hepatotoxicity consistently noted throughout the database. To estimate dietary risk from repeat exposure, the most suitable study is a 12-month oral (by capsule) toxicity study in the dog. A NOAEL of 0.5 mg/kg bw/day was established based on hepatotoxicity and a minimal effect on the adrenals in both males and females at the next dosage level of 5 mg/kg bw/day. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were used. With respect to the *Pest Control Products Act* factor, all of the required studies relevant to assessing risks to infants and children were available for this assessment. The degree of concern for pre- and post-natal toxicity was low since hepatotoxicity was the most sensitive endpoint with chronic exposure; therefore, the *Pest Control Products Act* factor was reduced to onefold.

$$\textbf{ADI} = \frac{\textbf{0.5 mg/kg bw/day}}{\textbf{100}} = \textbf{0.005 mg/kg bw/day}$$

This ADI provides a margin of 600 to the lowest NOAELs for developmental toxicity, teratogenicity and maternal toxicity. Also, there is a margin of 2000 to the NOAEL from the multigeneration reproduction study. It is thus considered protective of all populations including pregnant women, infants and children.

3.3.4 Chronic Dietary Exposure and Risk Assessment

The chronic dietary risk was calculated by using the average consumption of different foods and drinking water and the estimated residue values on those commodities. This expected intake of residues was then compared to the ADI. When the expected intake of residues is less than the ADI, then chronic dietary exposure is considered to be acceptable.

The chronic potential daily intake of tralkoxydim from food and water accounted for < 1% of the ADI for all subpopulations and is therefore, not of concern.

3.3.5 Cancer Potency Factor

See Section 3.2.2.

3.3.6 Carcinogenic Dietary Exposure and Risk Assessment

The cancer risk from dietary exposure (food and water) to tralkoxydim was 3.2×10^{-7} and is not of concern. A lifetime cancer risk that is below 1×10^{-6} usually does not indicate an unacceptable risk for the general population when exposure occurs through pesticide residues in or on food, and to otherwise unintentionally expose individuals.

3.4 Exposure from Drinking Water

3.4.1 Concentrations in Drinking Water

A Level 1 (least refined/unrefined) drinking water assessment was conducted using conservative assumptions with respect to environmental fate, application rate and timing and geographic scenario.

Residues of tralkoxydim in drinking water sources in Canada were estimated using Level 1 Leaching Estimation and Chemistry Model (LEACHM) and Pesticide Root Zone Model/Exposure Analysis Modeling System (PRZM/EXAMS). Leaching Estimation and Chemistry Model was used to estimate the residues in groundwater, whereas the residues in reservoirs and dugouts were estimated using Pesticide Root Zone Model/Exposure Analysis Modeling System. Leaching Estimation and Chemistry Model predicted that no residues will reach groundwater. For residues in reservoirs, the acute and chronic exposure concentrations predicted by Pesticide Root Zone Model/Exposure Analysis Modeling System were estimated to be 16.2 and 0.2 µg a.i./L, respectively. For residues in dugouts, the acute and chronic exposure concentrations predicted by Pesticide Root Zone Model/Exposure Analysis Modeling System were estimated to be 6.1 and 0.03 µg a.i./L, respectively.

3.4.2 Drinking Water Exposure and Risk Assessment

Drinking water exposure was considered in the acute and chronic non-cancer and cancer dietary assessments as both food and water consumption data and residue estimates were included in the assessments. For the acute assessment, residues in drinking water were based on the highest daily estimated environmental concentration (EEC) (16.2 ug a.i./L). In the chronic non-cancer and cancer assessment, residues in drinking water were based on the highest yearly EEC (0.3 ug a.i./L).

Risk to tralkoxydim from food and water were below the ARfD, ADI, and 1×10^{-6} for cancer risk. Therefore, the PMRA concludes that tralkoxydim residues in drinking water, when considered along with dietary exposure, are not of concern.

3.5 Aggregate Risk Assessment

Aggregate exposure is the total exposure to a single pesticide that may occur from food, drinking water, residential and other non-occupational sources as well as from all known or plausible exposure routes (oral, dermal and inhalation).

As tralkoxydim is not registered for residential and non-occupational uses, the aggregate risk assessment considered exposure from food and drinking only. Aggregate risk from all relevant sources is not considered a health concern (refer to Section 3.3 and Section 3.4).

3.6 Incident Reports

Starting 26 April 2007, registrants are required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Incidents are classified into six major categories including effects on humans, effects on domestic animals and packaging failure. Incidents are further classified by severity, in the case of humans for instance, from minor effects such as skin rash, headache, etc., to major effects such as reproductive or developmental effects, life-threatening conditions or death.

The PMRA will examine incident reports and, where there are reasonable grounds to suggest that the health and environmental risks of the pesticide are no longer acceptable, appropriate measures will be taken. The measures range from minor label changes to discontinuation of the product.

There were no incident reports submitted for tralkoxydim as of the 13 August 2008.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Tralkoxydim enters the terrestrial environment when it is used as a herbicide on a variety of grain cereals and forage grasses. In terrestrial environments, tralkoxydim is expected to biotransform rapidly (DT_{50} = 1 to 6 days). Compound 8 and 17 (refer to Appendix VIII), identified as major transformation products in soil under laboratory conditions, are expected to be slightly persistent (DT_{50} = 23–25 days) and non-persistent (DT_{50} = 7 days), respectively. Phototransformation of tralkoxydim may also contribute to the dissipation of tralkoxydim in the terrestrial environment; however, this has been established only for acidic soils where hydrolysis may be a contributing factor. The Henry's law constant (1.981×10^{-10} atm m^3/mole) indicates that tralkoxydim is not expected to volatilize from moist soil surfaces. Adsorption data indicate that tralkoxydim and the transformation products Compound 8 and 17 have the potential to be mobile in a variety of soils. The leaching assessment using groundwater ubiquity score (GUS)[5] indicates that tralkoxydim is a leacher under certain conditions; however, tralkoxydim does not satisfy all of the criteria set out by Cohen.[6] A soil column leaching experiment revealed low recoveries of tralkoxydim which was ascribed to extensive mineralization of residues to CO_2. Tralkoxydim is also shown to dissipate quickly under field conditions with no detection of residues below 10 cm soil depth

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5 Gustafson, D.I. (1989) Groundwater Ubiquity Score: A Simple Method for Assessing Pesticde Leachability. Environmental Toxicololgy Chemistry, 8: pp.339–357.

6 Cohen, S.Z., S.M. Creeger, R.F. Carsela nd C.G. Enfield (1984) Potential for Pesticide Contamination of Groundwater Resulting from Agricultural Uses. *In* R.F. Drugger and J.N. Seiber, editions., Treatment and disposal of Pesticide Wastes. ACS symposium Series Number 259. American Chemical Society, Washington, DC, pp.297–325.

beyond 30 days. Currently there is no monitoring data available to confirm or refute the presence of tralkoxydim in groundwater. Groundwater modeling, however, which utilized a scenario that would result in the conservative estimation of leaching, indicated that tralkoxydim does not reach groundwater. As a result, the PMRA does not consider tralkoxydim to be a significant concern regarding leaching.

Tralkoxydim has low solubility in water under acidic and neutral conditions (6 mg/L at pH 5.2 and 7 mg/L at pH 6.5) but is highly soluble under alkaline conditions (8850 mg/L at pH 9.0). Tralkoxydim can enter the aquatic environment through spray drift and runoff from the application site. Phototransformation will contribute to the dissipation of tralkoxydim from the water layer in the photic zone. Tralkoxydim is stable to hydrolysis at neutral and alkaline pH but may be an important route of transformation under acidic conditions.

Biotic transformation of tralkoxydim in the aquatic environment ranges from it being non-persistent to moderately persistent under aerobic conditions (DT_{50} = 5 to 154 days); in anaerobic systems, tralkoxydim is expected to be moderately persistent to persistent (DT_{50} = 91–204 days). Tralkoxydim has not been detected in surface water; however, Canadian water monitoring data of tralkoxydim is very limited.

The transformation products 3, 6 and 8 were identified as major transformation products in aquatic laboratory studies. The formation of Compound 3 and 8 as major transformation products, however, was observed in only one of three aquatic laboratory studies conducted with the same water-sediment system. Compound 6 is shown to primarily partition into sediment. Individual fate studies were not submitted to determine the persistence of the transformation products in aquatic conditions. DT_{50}s for the transformation products could not be determined from the parent studies because either no decline at study termination had occurred or the parent studies were of insufficient duration to fully track the rate of dissipation.

Based on the log K_{ow} of 2.1 for tralkoxydim, it is not expected to bioaccumulate in organisms. Environmental fate data for tralkoxydim and its transformation products is summarized in Appendix VII. A list of the major transformation products of tralkoxydim and their chemical structure is presented in Appendix VIII.

4.2 Effects on Non-target Species

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. Estimated environmental exposure concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential

differences in species sensitivity as well as varying protection goals (i.e. protection at the community, population or individual level).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms and to identify those groups of organisms, for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC = 1). If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

4.2.1 Effects on Terrestrial Organisms

A risk assessment of tralkoxydim to terrestrial organisms was based upon an evaluation of toxicity data on tralkoxydim to earthworms (acute contact), bees (acute oral and contact), two species of beneficial arthropods, three species of birds (acute oral and dietary), two species of mammals (acute oral, dietary and reproductive) and eighteen species of terrestrial plants (seedlings emergence, % visual damage, vegetative vigour). Toxicity data for the transformation products Compound 8 and 17 were also available for earthworms. A summary of terrestrial toxicity data for tralkoxydim and its transformation products is presented in Appendix IX. For the assessment of risk, toxicity endpoints chosen from the most sensitive species tested were used as surrogates for the wide range of species that can be potentially exposed following treatment with tralkoxydim.

Terrestrial Invertebrates
Tralkoxydim demonstrated no adverse toxicological effects on terrestrial invertebrates except in one earthworm toxicity study where a reduction in body weight was noted with an EC_{50} of 72 mg a.i./kg soil. Toxicity studies conducted with Compound 8 and 17 revealed no adverse toxicological effects to earthworms. No other toxicity studies for terrestrial organisms conducted with tralkoxydim transformation products were available for review.

Tralkoxydim is relatively non-toxic to honey bees according to the classification of Atkins et al (1981)[7] with acute contact and acute oral LD_{50}s being 49.9 µg a.i./bee and > 100 µg a.i./bee,

[7] Atkins EL; Kellum D; Atkins KW. 1981. Reducing pesticide hazards to honey bees: mortality prediction techniques and integrated management techniques. University of California, Div. Agric. Sci., Leaflet 2883. 22 p.

respectively. No sub-acute effects for bees were noted at any concentration tested in oral or contact studies. Acute contact toxicity studies for beneficial arthropods were also available. No mortality was recorded for ground beetles at 350 or 1750 g tralkoxydim/ha or wolf spiders at 350 g tralkoxydim/ha treatments.

The screening level risk assessment from tralkoxydim to terrestrial invertebrates is summarized in Appendix X. Exposure to the herbicide tralkoxydim is not expected to pose a risk to terrestrial invertebrates.

Terrestrial Plants

As tralkoxydim is a herbicide, adverse effects to non-target terrestrial plants are expected. Plant emergence and vegetative vigour studies conducted with 18 plant species indicated that, although the seeds of most plant species emerged successfully, plants did not follow normal growth patterns. The effects are likely due to the ability of tralkoxydim to inhibit the acetyl CoA carbozylase enzyme and so disrupt fatty acid synthesis.

The screening level risk assessment from tralkoxydim to terrestrial plants is summarized in Appendix X. Exposure to the herbicide tralkoxydim poses a risk to non-target terrestrial plants. The level of concern (LOC) was exceeded by 72 times at the single annual application rate (200 g a.i./ha). Less than 2% of the tralkoxydim application rate is expected to negatively affect non-target terrestrial plants (EC_{25} divided by the application rate). As a result, a refinement of the risk assessment was conducted taking into consideration the concentrations of tralkoxydim that could be present in terrestrial habitat directly adjacent to the application field through drift of spray. Spray drift data for a medium American Society of Agricultural Engineers (ASAE) droplet size indicate that the maximum amount of spray drift from ground and aerial application at one meter down wind from the point of application during spraying is 6 and 23%. Using these percent drift, the off-site EECs for tralkoxydim for ground and aerial application were calculated. Based on this method of refinement, tralkoxydim still poses a risk to non-target terrestrial plants directly adjacent to the application field. Exceedance of the LOC, however, was reduced to 4 and 17 times from 72 times for ground and aerial application rate (200 g a.i./ha), respectively. Buffer zones will be required to mitigate the risk of tralkoxydim to non-target terrestrial plants. The refined risk assessment from tralkoxydim to non-target terrestrial plants is summarized in Appendix XI.

Terrestrial Vertebrates

Mortality observed in some acute and dietary bird toxicity studies was limited to the highest exposure concentrations. Other non-lethal effects such as reduced feed consumption, reduced body weight and body-weight gain were also observed, however, in most cases birds recovered shortly after the exposure period. In bird reproduction studies, no significant treatment related effects were observed on reproductive parameters, food consumption or body weights at any of the test concentrations compared to the controls. Adverse effects were not readily apparent in most mammal studies, however, there were some effects on non-lethal parameters such as increased hepatic porphyrin accumulation in a dietary study using Swiss-mice and reduced parental body weight and body-weight gain, reduced litter weight and pupweight gain in a three generation reproduction study using rats.

The screening level risk assessment for tralkoxydim to birds and mammals is summarized in Appendix XII. For birds and mammals, the lowest toxicity endpoints (acute oral, dietary and reproduction) were used to extrapolate toxicity endpoints for birds and mammals of different sizes (20 g, 100 g and 1000 g for birds and 15 g, 35 g and 1000 g for mammals). To address differences in species sensitivity, the acute oral LD_{50} and dietary LC_{50}, converted to daily dose, was further divided by a safety factor of 10. The screening level assessment used relevant food categories representing specific feeding guilds for each bird and mammal size class consisting of 100% of a particular dietary item (plants, grain/seeds, insects and fruit). Estimated dietary exposures (EDE) for each bird and mammal size were calculated based on the estimated expected environmental concentrations (EECs) for each feeding preference group at each application rate and food ingestion rates. As no small birds and mammals in North America are known to eat a diet primarily of leafy plant material or grass, estimated dietary exposures for small birds (20 g and 100 g) and mammals (15 g) based on a 100% diet of plants were not calculated.

Exposure to tralkoxydim on an acute oral and dietary basis is expected to pose a negligible risk to birds or mammals. For birds, the level of concern (LOC) is exceeded for small 20 g insectivores and large sized herbivorous birds for reproductive effects (RQ = 1.2 and 1.7, respectively). For mammals, the LOC is exceeded for medium (35 g) and large (1000 g) sized herbivore mammals for reproductive effects (RQ = 1.7 and 3.2, respectively).

Given the conservative assumption taken in the screening level assessment, a refined assessment was conducted to further characterize the reproductive risk to insectivore and herbivore birds and herbivore mammals. An on-field assessment was conducted taking into consideration additional types of vegetation for the diet of herbivores. In addition, the risk associated with the consumption of food items contaminated from spray drift off the treated field was also assessed taking into consideration the spray drift deposition of spray quality of ASAE medium for ground (6%) and aerial application (23%) at 1 m downwind from the site of application.

Appendix XIII summarizes the refined risk assessment for tralkoxydim to birds and mammals respectively. The refined assessment shows that the reproduction LOC for birds and mammals feeding off-field is not exceeded. For the on-field assessment, the reproduction LOC is exceeded for small 20 g birds feeding on small insects and large 1000 g birds feeding on leaves and leafy crops, and short range grass (RQ = 1.1–1.7). For mammals feeding on-field the LOC is exceeded for small mammals of approximately 35 g feeding on all food types (except pods with seeds) and 1000 g feeding on leaves and leafy crops (RQ = 1.1–3.2).

The on-field assessment assumes a maximum exposure concentration on food items immediately after application, that mammals and birds would eat exclusively on a single food item (for example, short range grass) within the treated field and that the application timing coincides with the sensitive gestational period. Given that tralkoxydim is expected to dissipate quickly in the environment (for example, foliar half-life of 1.2 days), it is unlikely that a bird or mammal would eat exclusively on a single food item within the treated field and that it is unlikely that the timing of application would always coincide with the sensitive gestational period, the refined assessment is representative of a highly conservative scenario. In addition, for birds, the endpoint that was

used to determine reproductive risk (NOEC = 8.5 mg a.i./kg bw/day) is predicated on a study which showed no statistically significant effects at the highest test concentration. Use of this endpoint for the avian risk assessment, therefore, may greatly overestimate the reproductive risk to birds. Although the RQ values indicate a risk to small and large birds, as well as small mammals, this risk is not likely to manifest itself in the field.

4.2.2 Effects on Aquatic Organisms

Risk to aquatic organisms, acute and chronic, is based on an evaluation of toxicity data on tralkoxydim for six freshwater species (one invertebrate, two fish, two algal and one vascular plant). Some toxicity data on the transformation products were also available.

Aquatic organisms can be exposed to tralkoxydim as a result of drift and runoff. To assess the potential for effects from exposure to tralkoxydim and its transformation products, the screening level EECs in the aquatic environment based on direct application to water were used as exposure estimates. The calculated EECs were those determined in 15 cm body of water for amphibians and 80 cm body of water for all other aquatic organisms. A summary of aquatic toxicity data for tralkoxydim and its transformation products is presented in Appendix IX. For the assessment of risk, toxicity endpoints chosen from the most sensitive species tested were used as surrogates for the wide range of species that can be potentially exposed following treatment with tralkoxydim. The endpoints were derived by dividing the EC_{50} or LC_{50} from the appropriate laboratory study by a factor of two (2) for aquatic invertebrates and plants, and by a factor of 10 for fish and amphibians, (based on surrogate data from fish studies). The screening level risk assessment for tralkoxydim and its transformation products to aquatic organisms is summarized in Appendix XIV and XV, respectively.

Freshwater Organisms

Acute toxicity studies with Daphnia demonstrated mortality/immobility with a 48-hour LC_{50} >177 mg a.i./L and 2.7–163 mg a.i./L for the technical and formulated end-use products respectively. Mortality/immobility was observed in Daphnia exposed to Compound 17 (48-hour LC_{50} = 85 mg a.i./L) but not in Daphnia exposed to Compound 8 (48 hour LC50 >120 mg a.i./L). Reproductive effects in Daphnia were noted for technical tralkoxydim at a NOEC of 2.1 mg a.i./L for the number of live offspring. Exposure to Compound 6, a major transformation product predominantly present in the sediment phase, was shown to have no effect on the development of the sediment dwelling invertebrate (*Chironomus riparius*); NOEC = 63 mg a.i./kg dry sediment.

No mortality or symptoms of toxicity were observed in acute fish toxicity studies for technical tralkoxydim (96-hour LC_{50} = >7.2 to > 8.2 mg a.i./L). Some mortality and toxicity symptoms (for example, loss of balance, cessation of swimming), however, were noted in fish exposed to formulated end-use products (96-hour LC_{50} = 12–68 mg a.i./L). While acute exposure to Compound 17 resulted in no mortalities in fish at all concentrations tested (LC_{50} >120 mg a.i./L), mortality and toxicity symptoms (for example, loss of balance, twitching, cessation of swimming) were observed in fish exposed to Compound 8 (LC_{50} = 44 mg a.i./L).

Tralkoxydim did not adversely affect freshwater algae at the maximum concentrations tested (EC_{50} > 5.1 mg a.i./L). Tralkoxydim, as well as the transformation products Compound 8 and 17, however, significantly affected frond density and biomass in duckweed (*Lemna gibba*); the endpoints determined for acute exposure were EC_{50} = 1, 53 and 99 mg a.i./L, respectively.

The screening level risk assessment indicated that tralkoxydim is not a risk to freshwater invertebrates, fish, amphibians (based on surrogate data from fish studies), algae or plants. No risk was identified for freshwater invertebrates, fish, amphibians (based on surrogate data from fish studies) or plants exposed to Compound 17, invertebrates, fish and plants exposed to Compound 8 or sediment dwelling organisms exposed to Compound 6.

Marine and Estuarine Organisms

No data are available on the toxicity of tralkoxydim or its transformation products to marine and estuarine species of invertebrates, fish, algae or plants. According to use data provided by the registrant, tralkoxydim is predominantly used in the prairie and interior regions of British Columbia. Less than 0.1% of crops in Ontario and Quebec are treated with tralkoxydim, with no use being reported in the eastern Maritime Provinces. Should the use pattern for tralkoxydim change significantly, toxicity data for estuarine/marine species may be required.

5.0 Value

5.1 Commercial Class Products

5.1.1 Commercial Class Alternatives to Tralkoxydim

All tralkoxydim uses are supported by the registrants. There are no risk concerns for any of the registered uses. Consequently, the availability of alternatives to the use of tralkoxydim was not considered.

5.2 Domestic Class Products

There are no Domestic Class products containing tralkoxydim registered in Canada.

5.3 Value of Tralkoxydim

Tralkoxydim was first registered in Canada in 1992 and has been one of the widely used herbicides in cereal crop production since then. It is the only graminicide registered for use in perennial cereal rye in the year of crop establishment and in cereals underseeded to forage legumes such as alfafa, birdsfoot trefoil, sainfoin and clovers. Tralkoxydim can be tank-mixed with several broadleaf herbicides to broaden the spectrum of weed control. In addition, it can also be tank-mixed with insecticides for one pass weed and insect control.

Wild oats is one of the most troublesome weeds in cereal crop production. It is very competitive with barley and wheat and, if left unchecked, 10 wild oats per square metre can reduce barley and wheat yields by 10%. Tralkoxydim is one of the Group 1 graminicides registered for wild oats and annual grass control in cereal crops.

In Canada the estimated average annual losses caused by weeds were $291.3 million in wheat, $74.5 million in barley and $2.4 million in rye in the early 1990s. Tralkoxydim was reported to be used in these crops to prevent and reduce a portion of the economic losses incurred by weeds.

Consideration has to be given to the development of resistance in weeds associated with the use of tralkoxydim. Due to the widespread and frequent use of this graminicide, three resistant grassy weed biotypes have been documented in Canada including wild oats, green foxtail and Persian darnel. Nevertheless, tralkoxydim still plays a role in mitigating resistance development in weeds to other herbicide groups including Groups 2, 3, 8, 25 and 26.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The management of toxic substances is guided by the federal government's Toxic Substances Management Policy[8] (TSMP), which puts forward a preventive and precautionary approach to deal with substances that enter the environment and could harm the environment or human health. The policy provides decision makers with direction and sets out a science-based management framework to ensure that federal programs are consistent with its objectives. One of the key management objectives is virtual elimination from the environment of toxic substances that result predominantly from human activity and that meet persistence and bioaccumulation criteria. These substances are referred to in the policy as Track 1 substances.

During the review process, tralkoxydim was assessed in accordance with the PMRA Regulatory Directive DIR99-03,[9] *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*. Substances associated with the use of tralkoxydim were also considered, including transformation products formed in the environment and contaminants and formulants in the technical product and the end-use product.

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8 The federal Toxic Substances Management Policy is available through Environment Canada's web site www.ec.gc.ca/toxics.

9 The PMRA's Strategy for Implementing the Toxic Substances Management Policy, DIR99-03, is available through the Pest Management Information Service: Phone 1-800-267-6315 within Canada or 1-613-736-3799 outside Canada (long distance charges apply); Fax (613) 736-3798; e-mail pminfoserv@hc-sc.gc.ca or through our website at www.hc-sc.gc.ca/cps-spc/pest/index-eng.php.

Tralkoxydim and its transformation products were evaluated against the following Track 1 criteria:

- persistence in soil ≥182 days;
- persistence in water ≥182 days;
- persistence in sediment ≥365 days;
- persistence in air ≥2 days;
- bioaccumulation log K_{ow} ≥5 or BCF ≥5000 (or BAF ≥5000).

In order for tralkoxydim or its transformation products to meet Track 1 criteria, the criteria for both bioaccumulation and persistence (in one media) must be met. The technical product and end-use product, including formulants, were assessed against the contaminants identified in the *Canada Gazette*, Part II, Volume 139, Number 24, pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern, Part 3 Contaminants of Health or Environmental Concern.* The PMRA has determined that this active does not meet TSMP Track 1 criteria due to the following:

- Tralkoxydim does not meet the criteria for persistence as its half-life values in soil (1–5 days), are below the TSMP Track 1 cut-off criteria (182 days). Tralkoxydim does not meet the criteria for persistence in water under aerobic conditions as the maximum half-life value in aerobic water (154 days) is below the TSMP Track 1 cut-off criteria for water (182 days). However, tralkoxydim does meet the criteria for persistence in water under anaerobic conditions (204 days). The vapour pressure and Henry's law constant indicate that tralkoxydim will not volatilize from water or moist soil under field conditions, thus long-range atmospheric transport of tralkoxydim is not likely to occur.

- Tralkoxydim does not meet the Track 1 criterion for bioaccumulation, as its octanol-water partition coefficient (log K_{ow} = 2.1) is below the Track 1 criterion (log K_{ow} = 5.0).

- Technical grade tralkoxydim does not contain any by-products or microcontaminants that meet the TSMP Track 1 criteria. Impurities of toxicological concern are not expected to be present in the raw materials nor are they expected to be generated during the manufacturing process.

- The formulated products do not contain any formulants known to contain TSMP Track 1 substances.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, formulants and contaminants in the technical and end-use products are assessed against the formulants and contaminants identified in the *Canada Gazette*, Part II, Volume 139, Number 24, pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*. This list of formulants and contaminants of health and environmental concern are identified using existing policies and regulations including:

- the federal Toxic Substances Management Policy; the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol); and
- the PMRA Formulants Policy as described in the PMRA Regulatory Directive DIR2006-02, *Formulants Policy and Implementation Guidance Document*.

The *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* is maintained and used as described in the PMRA Notice of Intent NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act*.

The List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern consists of three parts:

- Part 1: Formulants of Health or Environmental Concern;
- Part 2: Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions; and
- Part 3: Contaminants of Health or Environmental Concern.

The contaminants to which Part 3 applies meet the federal Toxic Substances Management Policy criteria as Track 1 substances, and are considered in Section 6.1. The following assessment refers to the formulants and contaminants in Part 1 and Part 2 of the list.

Technical grade tralkoxydim and its end-use products do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*, Part II, Volume 139, Number 24, pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for tralkoxydim is adequate to define the majority of toxic effects that may result from exposure to tralkoxydim. In rats, there was evidence of carcinogenicity in the form of benign Leydig-cell tumours in males and uterine adenocarcinomas in females. In female hamsters, benign liver tumours, uterine tumours and ovarian tumours were noted. There was no treatment-related increase in the number of tumours in male hamsters.

Tralkoxydim was not genotoxic and induced no signs of neurotoxicity. Tralkoxydim was teratogenic at a level that resulted in severe maternal toxicity in both rats and rabbits. The main target of toxicity for all species evaluated was the liver. At higher dose levels the endocrine organs also appear to be targeted by tralkoxydim. When tralkoxydim was given to pregnant animals, effects on the developing fetus were observed at doses that were toxic to the mother, indicating that the fetus is not more sensitive to tralkoxydim than the adult animal. The risk assessment protects against these effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

7.1.1 Occupational Risk

Cancer and non-cancer risk estimates associated with mixing and loading and applying tralkoxydim are not of concern provided the personal protective equipment in Section 8.1.1 is added to all labels. Postapplication cancer and non-cancer risks to workers are not of concern; the minimum 12-hour restricted-entry interval (REI) is proposed for all uses.

7.1.2 Dietary Risk from Food and Water

Acute and chronic non-cancer and cancer risk estimates associated with exposure of tralkoxydim from food are not of concern.

7.1.3 Dietary Risk from Drinking Water

Acute and chronic non-cancer and cancer risk estimates associated with exposure of tralkoxydim from water are not of concern.

7.1.4 Residential Risk

There are no residential uses of tralkoxydim.

7.1.5 Aggregate Risk

Aggregate exposure is the total exposure to a single pesticide that may occur from food, drinking water, residential and other non-occupational sources, as well as from all known or plausible exposure routes (oral, dermal and inhalation).

As tralkoxydim is not registered for residential or non-occupational uses, the aggregate risk assessment considered exposure from food and drinking only. Aggregate risk from all relevant sources is not considered a health concern (refer to Section 3.3 and Section 3.4).

7.2 Environmental Risk

Tralkoxydim is non-persistent in soils and is non-persistent to persistent in aquatic systems. Tralkoxydim and its major transformation products Compound 8 and 17 have the potential to be mobile in the environment. Therefore, under appropriate conditions tralkoxydim, Compound 8

and 17 may through runoff, appear in surface water. A screening level risk assessment indicates that tralkoxydim is not a risk to aquatic organisms, even if it is directly applied to water. In addition, Canadian water monitoring data although limited, shows no detection in surface water. As such, runoff is not expected to be a concern to aquatic life. Tralkoxydim use is not a concern for terrestrial organisms except for terrestrial plants. The risk assessment for non-target terrestrial plants indicates that spray drift will have adverse effects on non-target plants. However, these effects can be mitigated by the regulatory actions indicated below.

7.3 Value

From the value perspective, tralkoxydim is acceptable for continued registration.

8.0 Proposed Regulatory Decision

The PMRA is proposing that tralkoxydim is acceptable for continued registration with the implementation of the proposed risk-reduction measures. These measures are required to further protect human health and environment. As a condition of the continued registration of tralkoxydim uses, new risk-reduction measures must be included on the labels of all products.

8.1 Proposed Regulatory Action Related to Human Health

The PMRA has determined that the dietary and drinking water risks and risks to workers during mixing, loading, application and postapplication activities are acceptable, provided that the mitigation measures listed in this section are implemented.

8.1.1 Proposed Regulatory Action Related to Occupational Handlers

The following mitigation measures are required for all commercial class products containing tralkoxydim:

- Only one application is permitted per season;
- Workers must wear coveralls over long-sleeved shirt, long pants and chemical resistant gloves when mixing, loading and during clean-up, or when adjusting or repairing the sprayer;
- Applicators must wear long-sleeved shirt and long pants; and
- Restricted-entry interval (REI) of 12 hours.

There may be potential for exposure to bystanders from drift following pesticide application to agricultural areas. As the risks for postapplication workers did not require mitigation on day 0, bystander risks are anticipated to not be of concern. However, to promote best management practices and to minimize human exposure from spray drift or from spray residues resulting from drift, the following label statement is required:

> "Apply only when the potential for drift to areas of human habitation or areas of human activity such as houses, cottages, schools and recreational areas is minimal. Take into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings."

8.1.2 Residue Definition for Risk Assessment and Enforcement

Based on plant and animal metabolism studies, the residue definition in plant commodities is the parent, tralkoxydim. For animal commodities a residue definition is not required as negligible residues are expected to occur in livestock. The dietary risk assessment considered potential residues in animal commodities by incorporating anticipated residue estimates, which were based on data from animal metabolism studies and the maximum dietary burden (MTDB).

8.1.3 Maximum Residue Limits for Tralkoxydim in Food

In general, when the re-evaluation of a pesticide has been completed, the PMRA intends to update Canadian MRLs and to remove MRLs that are no longer supported. The PMRA recognizes, however, that interested parties may want to retain an MRL in the absence of a Canadian registration, to allow legal importation of treated commodities into Canada. The PMRA requires similar chemistry and toxicology data for such import MRLs as those required to support Canadian food use registrations. In addition, the PMRA requires residue data that are representative of use conditions in exporting countries, in the same manner that representative residue data are required to support domestic use of the pesticide. These requirements are necessary so that the PMRA may determine whether the requested MRLs are needed, and to ensure they would not result in unacceptable health risks.

After the revocation of an MRL or where no specific MRL for a pest control product has been established in the *Pest Control Products Act*, subsection B.15.002(1) of the *Food and Drug Act* applies. This requires that residues do not exceed 0.1 ppm and has been considered a general MRL for enforcement purposes. Currently, residues of tralkoxydim in rye and triticale are regulated by subsection B.15.002(1). However, changes to this general MRL may be implemented in the future as indicated in Discussion Document DIS2006-01, *Revocation of 0.1 ppm as a General Maximum Residue Limit for Food Pesticide Residues [Regulation B.15.002(1)]*.

As indicated in Table 8.1.3, the *Pest Control Products Act* specifies MRLs for tralkoxydim residues in wheat and barley. Residues in all other agricultural commodities, including those approved for treatment in Canada but without a specified MRL (i.e. rye and triticale) must not exceed the general MRL of 0.1 ppm.

Residue data were available to indicate the existing MRLs should not be exceeded if tralkoxydim is used according to good agricultural practice (GAP), as described by the current product labels.

There were no residue data on file for rye and triticale. The technical registrant is required to provide this data. Extrapolation of available residue data for wheat and barely indicated that residues should not exceed the 0.1 ppm general MRL in cereal commodities if tralkoxydim is used according to good agricultural practice.

Parties interested in supporting a tralkoxydim MRL should contact the PMRA during the comment period of this document to discuss the submission of appropriate data.

Table 8.1.3 Tralkoxydim MRLs for Commodities Approved for Treatment in Canada and for Import Commodities with Specified MRLs

Commodity	Maximum Residue Limit
Wheat	0.02
Barley	0.02
Rye	0.1*
Triticale	0.1*

* By virtue of subsection B.15.002(1) of the Food and Drug Regulations, the maximum residue limit of foods for which MRLs have not specifically been established is 0.1 ppm.

8.2 Proposed Regulatory Action Related to Environment

To reduce the effects of tralkoxydim in the environment, mitigation in the form of precautionary label statements and buffer zones are required. Environmental mitigation statements are listed in Appendix XVII.

List of Abbreviations

a.i.	active ingredient
ADI	acceptable daily intake
ALS	acetolactate synthase
ARfD	acute reference dose
ASAE	American Society of Agricultural Engineers
atm	atmospheres
bw	body weight
cm	centimetre(s)
CoA	acetyl coenzyme A
d	day(s)
DEEM®	Dietary Exposure Evaluation Model
DER	Data Evaluation Report
DFR	dislodgeable foliar residue
DNA	deoxyribonucleic acid
DT_{50}	dissipation time to 50% (the dose required to observe a 50% decline in the test population)
EC_{25}	exposure concentration to 25% (a concentration causing 25% adverse effects in the test population
EC_{50}	exposure concentration to 50% (a concentration causing 50% adverse effects in the test population
EChE	erythrocyte cholinesterase
EDE	estimated daily exposure
EEC	expected environmental concentration
EP	end-use product
EPA	Environmental Protection Agency (United States)
EXAMS	Exposure Analysis Modeling System
F_0	parental animals
F_1	first filial generation
g	gram(s)
GAP	good agricultural practice
GC-FPD	Gas Chromatography-Flame Photometric Detector
GC-MSD	Gas Chromatography-Mass Selective detector
GC-NPD	Gas Chromatography-Nitrogen Phosphorous Detector
h	hour(s)
ha	hectare(s)
Hg	mercury
K_d	adsorption coefficient
kg	kilogram(s)
K_{oc}	organic carbon partition coefficient
K_{ow}	*n*-octanol–water partition coefficient
L	litre(s)
LC_{50}	lethal concentration to 50% (a concentration causing 50% mortality in the test population

LD_{50}	lethal dose to 50% (a dose causing 50% mortality in the test population)
LOAEL	lowest observed adverse effect level
LOC	Level of Concern
LOD	limit of detection
LOEC	lowest observed effect concentration
m	metre(s)
m/sec	metre(s) per second
m^3	metre(s) cubed
mg	milligram(s)
µg	microgram(s)
mL	millilitre(s)
mm	millimetre(s)
MOE	margin of exposure
nd	no detection
nm	nanometre(s)
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
OC	organic carbon
OM	organic matter
PChE	plasma cholinesterase
PCP	Pest Control Product
PDP	Pesticide Data Program (United States data)
pH	-log10 hydrogen ion concentration
PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
PMRA	Pest Management Regulatory Agency
PPE	personal protective equipment
ppm	parts per million
PRZM	Pesticide Root Zone Model
Q_1^*	cancer potency factor
REI	restrictedentry interval
RQ	risk quotient
TC	transfer coefficient
TGAI	technical grade active ingredient
TP	transformation product
TSMP	Toxic Substances Management Policy
URMULE	User Requested Minor Use Label Expansion
US	United States
USEPA	United States Environmental Protection Agency
wk	week
yr	year
°C	degree(s) Celsius

Appendix I Registered tralkoxydim products as of 28 August 2008[1]

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee
22413	Technical	Syngenta Crop Protection Canada Incorporated	Tralkoxydim Technical	Solid	98.1%
27011	Commercial	Syngenta Crop Protection Canada Incorporated	Achieve Liquid Herbicide	Suspension	400 g/L
27579	Commercial	Dow AgroSciences Canada Incorporated	Prevail A Liquid Herbicide (A Component of Prevail Liquid Herbicide Tank-Mix)	Suspension	400 g/L
27596	Technical	Syngenta Crop Protection Canada Incorporated	Tralkoxydim Technical Wet Paste	Paste	83.8%
28536	Commercial	Dow AgroSciences Canada Incorporated	Baseline A Herbicide (A Component of Baseline Herbicide Tank-Mix)	Suspension	400 g/L
28555	Commercial	Dow AgroSciences Canada Incorporated	Liquid Achieve SC Herbicide	Suspension	400 g/L
28664	Commercial	Syngenta Crop Protection Canada Incorporated	Achieve 10SC Herbicide	Suspension	400 g/L

[1] Excluding discontinued products or products with a submission for discontinuation

Appendix II Registered Commercial Class uses of tralkoxydim in Canada as of 13 June 2008[1]

Use Site Category	Sites		Weeds[2]	Application Equipment	Supported Uses?[3]
13, 14 Terrestrial feed crops and terrestrial food crops	Cereal crops (spring wheat, winter wheat, durum wheat, barley, triticale, spring rye and winter rye) grown alone or underseeded to forage legumes: alfalfa, birdsfoot trefoil, sainfoin and clovers	Across Canada	A plus barnyard grass	Ground application equipment; aerial application equipment (fixed-wing or rotary aircraft equipment)	Y
		Eastern Canada	Wild oats		
13, 14 Terrestrial feed crops and terrestrial food crops	Spring wheat, durum wheat and barley underseeded with legumes	Prairie provinces and Peace River region of British Columbia	A plus B	Ground equipment only	
	Spring wheat, durum wheat and barley not underseeded with legumes		A plus C		
13 Terrestrial feed crops	Seedling and established intermediate and crested wheatgrass, creeping red fescue, and meadow and smooth bromegrass either underseeded to seedling and established intermediate and crested wheatgrass, creeping red fescue, and meadow and smooth bromegrass underseeded to cereals or grown alone (for seed production purposes only) For establishment of northern wheatgrass, western wheatgrass, and slender wheatgrass (for seed production purposes only)	Across Canada	A		Y, M
	For perennial cereal rye in the year of crop establishment	Prairie provinces only			

[1] The formulation type for all supported end-use products is suspension. Application is made once per year at a maximum application rate of 200 g a.i./ha. Information on application equipment and the number of applications is based on both label use information and information provided by the registrant. Uses of tank-mix products are not presented.

[2] A = Wild oats, volunteer tame oats, green foxtail, yellow foxtail and Persian darnel.
B = Canada thistle (season-long control, with some regrowth in the fall), redroot pigweed, dandelion (spring rosettes only), scentless chamomile (2 to 4 leaf), wild mustard, flixweed (spring rosettes only), shepherd's-purse (spring rosettes only), kochia (suppression at 2 to 4 leaf stage), smartweed, lamb's-quarters, stinkweed (spring rosettes only), annual sow-thistle, perennial sow-thistle (top growth), tartary buckwheat, wild buckwheat, common groundsel, volunteer rapeseed and Russian pigweed.
C = Barnyard grass, cleavers, kochia (including biotypes resistant to Group 2 herbicides that inhibit the ALS/AHS enzyme), volunteer flax, Stork's bill (suppression).

[3] Y = Use is currently registered and supported by the registrant; M = Use was registered as a User Requested Minor Use Label Expansion (URMULE).

Appendix IIIA Toxicology Profile for Tralkoxydim

NOTE: Effects noted below are known or assumed to occur in both sexes unless otherwise specified.

Study/Species/ Number of Animals per Group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Metabolism/Toxicokinetic Studies			
Metabolism/ Toxicokinetic Study–rats	• [^{14}C]-tralkoxydim administered by gavage (in corn oil), repeat (14 days) and acute exposures of 1 and 40 mg/kg bw • Unlabelled: 97.8% purity; radiolabeled: >94.3% purity		**Absorption**: Tralkoxydim was rapidly absorbed. Whole body autoradiography showed that the majority of radiolabel was associated with the alimentary tract at 5 hours. The concentration in the blood was high, particularly in males, thus causing a general distribution of radiolabel. At 48 hours, very little radiolabel was present. Most of the remaining radiolabel was still associated with intestinal contents (♂) or with the liver, the cortex and the corticomedullary region of the kidney (♀). **Distribution**: Concentrations in liver, kidney, fat and blood at 7 days were low (<0.03%) and were unaltered by repeat dosing. **Metabolism**: Proposed metabolic pathway: metabolism of tralkoxydim primarily involved oxidation of the methyl groups of the trimethylphenyl moiety with tralkoxydim alcohol (<20% of dose, excreted via urine) being the primary product, this was further oxidized to give tralkoxydim diol (10% of dose, urine of ♂ but not found in urine of ♀) or tralkoxydim acid (50–85% of dose, most initially excreted by bile). These three metabolites accounted for ~ 90% of the metabolites found in the bile and urine. Some additional metabolism at the imino portion of the molecule formed minor metabolites tentatively identified as tralkoxydim alcohol oxazole, tralkoxydim acid oxazole and tralkoxydim diol oxazole (<10%). Unchanged parent compound was identified in the feces and bile but not in the urine. Repeat dosing did not significantly alter the formation of metabolites.
			Excretion: By 72 hours, virtually all of the radiolabel was excreted. *Males*: 55–66% of the radiolabel was excreted in urine and 30–36% in feces over 24–48 hours. *Females*: 30–44% of the radiolabel was excreted in urine and 19–48% in feces over 24–48 hours. There was no detectable radioactivity in expired CO_2. ***Cannulated Bile Ducts***: **Excretion**: Approximately 10% of the dose was found in urine and 1.5–2.0% in feces over 48 hours. 78% and 64% was found in bile in males and females respectively, at 48 hours.

Study/Species/ Number of Animals per Group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Metabolism/ Toxicokinetic Study- hamsters	• Single oral dose of 1 mg/kg bw [^{14}C]-phenyl uniformly ring-labelled tralkoxydim in corn oil by gavage • Purity N/S		**Distribution**: Organ concentrations at 7 days were low with the highest amount found in liver (≤0.04%). **Metabolism**: Tentative identifications of the major peaks in urinary chromatograms were consistent with tralkoxydim acid and lesser amounts of the tralkoxydim acid oxazole. **Excretion**: Recoverable residues were fourfold higher in urine than in feces for either sex.
Pharmacokinetics following a single oral dose in humans (7♂ volunteers)	• 5 mg tralkoxydim (in corn oil), provided in gelatin capsules • Purity N/S		Tralkoxydim acid in urine constituted about 41–71% of the administered dose. Assays of tralkoxydim acid in blood (sample preparation not described) reported no measurable residues. **Considered supplemental.**
Acute Toxicity Studies			
Acute Oral Toxicity–Rats (5/sex/dose)	• ♂ : 500–1800 mg/kg bw (in corn oil); ♀: 500–1000 mg/kg bw (in corn oil) • 97.8% purity		**LD_{50} = 1258/934 mg/kg bw (♂/♀)** **Moderate Toxicity.**
Acute Oral Toxicity–Mice (5/sex/dose)	• 500–2,000 mg/kg bw (in corn oil) • 97.8% purity		**LD_{50} = 1231/1100 mg/kg bw (♂/♀)** **Slight Toxicity.**
Acute Oral Toxicity–Rabbits (3♂/group)	• 48.9–519 mg/kg bw (in corn oil) • 97.8% purity		**LD_{50} > 519 mg/kg bw** **Considered supplemental.**
Acute Dermal Toxicity–Rats (5/sex/group)	• 2000 mg/kg bw for 24 hours under an occlusive dressing • 99% purity		**LD_{50} > 2000 mg/kg bw** **Considered supplemental due to methodology.**
Acute Inhalation Toxicity–Rats (5/sex/group)	• 0, 0.4 or 3.5 mg/L air for four hours (nose only) • 97.3% purity		**LC_{50} > 3.5 mg/L** **Low toxicity.**
Dermal Irritation–Rabbits	• 500 mg (in olive oil) under occlusive		**Mild irritant.**

Study/Species/ Number of Animals per Group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
(6♀/group)	dressing for four hours • 97.8% purity		
Acute Eye Irritation–Rabbits (6♀/group)	• 100 mg (~25–33% test material displaced from conjunctival sac immediately following application) • 97.8% purity	**Mild irritant.**	
Dermal Sensitization–Guinea-pigs • Magnusson and Kligman maximization test (Control: 10♂; Test: 20♂)	• 5% in corn oil for intradermal application, 75% in corn oil for topical application • 97.8% purity	No evidence of dermal sensitization. **Considered supplemental (induction dose insufficient).**	
Subchronic Toxicity Studies			
28-day Dietary Toxicity Study–C57BL/10JF CD-1 mice (5/sex/dose)	• 0, 50, 250, 1250 or 5,000 ppm (0, 7.5, 37.5, 188 or 750 mg/kg bw/day) in diet • subsequent 28-day study: 0, 2, 10 or 25 ppm (0, 0.3, 1.5 or 3.8 mg/kg bw/day) in diet • 97.8% purity	1.5	≥3.8 mg/kg bw/day: hepatic focal or multi focal areas of necrosis, hyperplasia and fibrosis of the bile ducts with an associated inflammatory reaction accompanied by pigment accumulation in the bile ducts and Kupffer cells (indicative of protoporphyrin); ≥7.5 mg/kg bw/day: absolute and relative liver weights (♂); ≥187.5 mg/kg bw/day: ↓ body weight and body-weight gain, electron microscopy revealed the presence of small crystalline aggregates in the lumen of some bile ducts, cytoplasm of hepatocytes and Kupffer cells/periportal macrophages, hepatocellular vesiculation of SER, marked mitochondrial swelling and enlargement of hepatocytes, bile duct proliferation, ↑ prevalence of macrophages and other inflammatory cells in periportal areas of the liver, ↑ collagen and fibroblasts; mitochondrial swelling (♀); 750 mg/kg bw/day: ↓ body weight, body-weight gain and food consumption, ↑ proliferation of SER in centrilobular hepatocytes; ↑ relative liver weights (♀).

Study/Species/ Number of Animals per Group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
			*Special staining techniques designed to demonstrate the presence of iron, bile, calcium and lipofuscin did not reveal any treatment-related effects.
28-day Dietary Toxicity Study–3 strains of mice [C57BL/10Jf CD-1 (BL/10), CD-1(AP) and BALB/c] (10/sex/dose)	• 0, 25 or 125 ppm •(≈ 0, 3.8 or 18.8 mg/kg bw/day) in diet •92.4% purity	LOAEL (all strains) = 3.8	All strains unless otherwise specified: ≥3.8 mg/kg bw/day: ↑ cholesterol (BALB/c, BL/10 and AP ♀), ↑ absolute (BALB/c ♂, AP ♀) and relative (BALB/c ♂, BL/10 ♀, AP) liver weights, ↑ plasma bile acids (BALB/c ♀, BL/10), ↑ ALT (BALB/c, BL/10), ↑ total liver porphyrin levels, enlarged livers with dark brown discolouration, biliary hyperplasia, biliary fibrosis, eosinophilic change of bile duct epithelium, brown birefringent pigment (indicative of porphyrin) deposition in hepatocytes, bile ducts and Kupffer cells, ↑ hepatocytic mitotic rate, portal inflammation and necrosis of hepatocytes; 18.8 mg/kg bw/day: ↓ food consumption (AP), ↑ cholesterol (AP ♂), ↑ ALP (BALB/c, BL/10), ↑ plasma bile acids (BALB/c ♂, AP ♀), ↑ ALT (AP), ↑ absolute (BALB/c ♀, BL/10, AP ♂) and relative (BALB/c ♀, BL/10 ♂) liver weights.
90-day Dietary Study–Syrian hamsters (20/sex/dose)	• 0, 250, 800, 2000 or 5000 ppm (≈ 0, 18, 55, 140 or 350 mg/kg bw/day) via the diet • following a 29-day interim kill (8/sex/dose), a satellite group was started where animals (10/sex/dose) were fed 0, 10 000 or 20 000 ppm (≈ 0, 700 or 1400 mg/kg bw/day) for up to 90 days (with and interim kill of 5/sex/dose on day 30) • Main Study: 92.8% purity; Satellite Study: 94.9% purity	LOAEL = 350	***Main Study***: 350 mg/kg bw/day: transient ↑ in SER volume in centrilobular hepatocytes, ↓ lymphocytes, ↑ relative liver weights; loss of hepatocyte vacuolation (♂) ***Satellite Study***: ≥700 mg/kg bw/day: ↓ body-weight and body-weight gain, ↓ food consumption, ↓ Hgb, Hct and RBC, ↓ cholesterol, ↑ relative liver weights,↑ hepatocyte eosinophilia graded as slight, ↑ SER volume and proliferation in centrilobular hepatocytes (5/5♂, 2/5♀); ↓ food efficiency (♂); ↑ liver porphyrin levels, loss of hepatocyte vacuolation, ↑ incidence of renal nephropathy (♀); 1400 mg/kg bw/day: ↓ body weight and body-weight gain, ↑ MCH, ↑ plasma triglycerides, ↑ absolute liver weights, ↑ SER volume and proliferation, small vesicles/pale lipid-like material budding from SER, swollen bile canaliculi with small deposits of electron

Study/Species/ Number of Animals per Group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
			dense fibrillar material (phospholipid), kidneys with pitted or roughened surfaces; ↑ relative kidney weights, ↑ liver porphyrin levels (♂); ↑ ALP, ↑ triglycerides, ↑ hepatocyte eosinophilia graded as moderate (4/5), ↑ SER volume and proliferation in centrilobular hepatocytes (5/5) (♀). * Histopathology was carried out on the controls, 350, 700 and 1400 mg/kg bw/day animals.
90-day Dietary Toxicity Study–Wistar rats (20/sex/dose)	• 0, 50, 250 or 2500 ppm (= 0/0, 4.2/4.6, 20.5/23.0 or 205/220 mg/kg bw/day ♂/♀) in diet • 97.8% purity	20.5/23.0 (♂/♀)	≥4.2/4.6 mg/kg bw/day (♂/♀): slightly ↑ WBC and lymphocytes (♂) (not considered adverse); >20.5/23.0 mg/kg bw/day (♂/♀): ↓ plasma triglyceride levels (not considered adverse) (♂); ↓ plasma cholesterol levels (not considered adverse) (♀); 205/220 mg/kg bw/day: ↓ body-weight gain, ↓ food consumption, ↓ Hgb and Hct, ↑ ALT, ↑ plasma albumin levels, ↓ absolute adrenal weights, ↓ absolute and relative kidney weights, ↑ relative liver weights, ↓ absolute lung weights; ↑ WBC, ↑ AST, ↑ ALP, ↓ plasma triglyceride, cholesterol and eosinophils (♂); ↑ lymphocytes, ↓ RBC and neutrophils (♀).
90-day Oral (capsule) Toxicity Study–Beagle dogs (4/sex/dose)	• 0, 0.5, 5 or 50 mg/kg bw/day by capsule • 97.8% purity	5	0.5 mg/kg bw/day: ↓ creatine kinase activities (no dose–response relationship, not considered adverse) (♂); slightly ↑ hepatic aminopyrine N-demethylase activities (APDM) (not considered adverse) (♀) ; 5 mg/kg bw/day: ↑ absolute liver weights, ↓ creatine kinase activities (no dose–response relationship), ↑ hepatic APDM (all effects not considered adverse) (♂); 50 mg/kg bw/day: ↓ Hgb, Hct and RBC, ↑ platelets and WBC, ↑ ALP and ALT activities, ↓ albumin, total protein, cholesterol and triglycerides, ↑ plasma urea levels, ↑ hepatic APDM, ↑ absolute liver and adrenal weights, enlarged pale livers with marked reticular pattern, slight to marked fatty change mainly in the periportal region of the liver, minimal to

Study/Species/ Number of Animals per Group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
			slight vacuolation of cells in the *zona fasciculata* of the adrenals with a multifocal distribution, proliferation of SER in centrilobular hepatocytes (more marked in ♀); ↑ neutrophils, ↓ creatine kinase activities, ↓ epididymal weights, minimal unilateral atrophy of seminiferous epithelium (♂); ↑ prothrombin and kaolin-cephalin times, ↓ plasma calcium levels, concentric lamellar bodies (composed of modified SER) in hepatocytes (♀). The smooth endoplasmic reticulum (SER) and peroxisome volume of the cytoplasm of these cells were determined using a point counting technique. There was no evidence of an increased number of peroxisomes.
12-month Oral (capsule) Toxicity Study–Beagle dogs (4/sex/dose)	• 0, 0.5, 5 or 50 mg/kg bw/day by gelatin capsule • 94.9% purity	0.5	≥5 mg/kg bw/day: ↑ ALP and ALT activity, greenish-black deposits and discoloured mucosa in the gall bladders; moderate periportal fatty liver, ↑ relative adrenal weights (♂); minimal vacuolation of zona fasciculata and reticularis of the adrenal glands, ↑ plasma urea, ↓ plasma cholesterol, triglycerides and potassium (♀); 50 mg/kg bw/day: ↑ MCV, ↓ plasma albumin and total protein levels, ↑ prothrombin times, ↑ absolute and relative liver, adrenal and thyroid weights, gross hepatic findings (enlarged, mottled, friable and swollen lobes with and accentuated lobular pattern), diffuse or periportal fatty changes of the liver, moderate or marked vacuolation of zona fasciculata and reticularis of the adrenal glands; ↓ RBC, Hgb and Hct, ↓ plasma cholesterol and triglycerides, ↑ platelets, ↑ ALP, minimal epididymal interstitial lymphoid infiltration, unilateral tubular degeneration of the testes (one) (♂); ↑ MCH, ↑ WBC, ↓ plasma creatine kinase activities (♀). * Epididymal weights were not investigated.

Chronic Toxicity/Oncogenicity Studies			
18-month Dietary Toxicity Study–Syrian hamsters (72/sex/dose, with 3 control groups used (i.e. 216 animals/sex) due to a lack of historical information regarding this species)	• 0, 250, 2500 or 7500 ppm (= 0/0, 14.9/14.8, 153/148 or 439/428 mg/kg bw/day ♂/♀) via the diet • 97.6% purity	14.9/14.8 (♂/♀)	≥153/148 mg/kg bw/day (♂/♀): ↑ lipofuscin pigment in the hepatocytes, ↓ food consumption, ↓ WBC and lymphocytes (♂); ↑ body-weight gain, ↑ incidence of urinary incontinence and abnormal respiratory noise, ↑ incidence of lipofuscin pigment in Kupffer cells (♀); 439/428 mg/kg bw/day (♂/♀): ↓ food consumption, ↑ incidence of diarrhea and abnormal respiratory noise, ↑ MCHC, ↑ amount of lipofuscin accumulation within hepatocytes; ↓ body-weight gain, ↓ food efficiency, ↑ absolute and relative liver and testicular weights (♂); ↑ body-weight gain, ↓ absolute and relative kidney weights, ↑ incidence of urinary incontinence and minimal golden cortical pigmentation in the adrenal glands (♀). ***Neoplastic effects***: Benign adrenal gland cortical adenomas (♀): 0/72, 1/72, 1/72, 2/72, 4/70 and 4/72 at 0, 0, 0, 14.8, 148 or 428 mg/kg bw/day, respectively Malignant adrenal gland cortical adenocarcinomas (♀): 0/72, 0/72, 1/72, 0/72, 2/70 and 0/72 at 0, 0, 0, 14.8, 148 or 428 mg/kg bw/day, respectively The survival of Syrian hamsters in this study (median survival: ♂–77 weeks; ♀–53 weeks) was not inconsistent with survival data from other labs. This study was deemed acceptable for the assessment of chronic toxicity in a second rodent species. However, there were limitations in assessing the potential carcinogenicity of tralkoxydim due to the high mortality noted in all females. As a result, no definitive conclusions concerning cancer can be made.
80-week Dietary Carcinogenicity Study–Syrian hamsters (51/sex/dose)	• 0, 500, 2500 or 12 000 ppm (=0/0, 29.5/27.8, 150.3/138.9 or 700.3/672.2 mg/kg bw/day ♂/♀) via the diet • 98.2% purity	150.3/27.8 (♂/♀)	**Males**: 150.3 mg/kg bw/day: ↓ food efficiency, ↓ WBC, neutrophils and monocytes (not considered adverse); 700.3 mg/kg bw/day: ↓ body weight, body-weight gain, food consumption and food effeciency, ↑ absolute and relative liver, kidney and testicular weights, ↑ incidence of cortical cysts of the adrenal gland (6/51 as compared to 2/50 in controls) and mononuclear cell infiltration of the

			liver (9/51 as compared to 4/51 in controls). **Females**: 138.9 mg/kg bw/day: ↑ absolute liver weights; ↑ incidence of endometrial hyperplasia of the uterus (6/51 as compared to 2/51 in controls), cysts of the thymus (4/36 as compared to 1/37 in controls) and ovarian cysts (10/48 as compared to 3/49 in controls); 672.2 mg/kg bw/day: ↓ food consumption, ↑ absolute and relative liver and ovarian weights, ↓ absolute and relative uterine weights, ↑ incidence of endometrial hyperplasia of the uterus (6/51 as compared to 2/51 in controls), cysts of the thymus (4/39 as compared to 1/37 in controls), ovarian cysts (6/51 as compared to 3/49 in controls), glandular dilatation of the uterus (14/51 as compared to 9/51 in controls) and increased pigmentation of the liver (6/51 as compared to 3/51 in controls). **Neoplastic Effects:** ***Hepatocellular adenomas***: ↑ incidence in high-dose ♀ (0/51, 0/51, 0/51 and 3/51 at 0, 27.8, 138.9 and 672.2 mg/kg bw/day, respectively). ***Adenoma of the uterus***: ↑ incidence in high-dose ♀ (0/51, 0/51, 0/51 and 2/51 at 0, 27.8, 138.9 and 672.2 mg/kg bw/day, respectively). ***Benign sex cord stromal tumours of the ovary***: ↑ incidence in ≥mid-dose ♀ (1/49, 2/50, 4/48 and 5/51 at 0, 27.8, 138.9 and 672.2 mg/kg bw/day, respectively). **Tralkoxydim is considered to be tumourigenic in female hamsters.**
Two year Chronic/ Carcinogenicity Dietary Toxicity Study–Wistar rats (64/sex/dose; 12/sex/group were killed at week 53)	• 0, 50, 500 or 2500 ppm (= 0/0, 2.3/3.0, 23.1/30.1 or 118/163 mg/kg bw/day ♂/♀) via the diet • 92.4% purity	NOAEL (systemic) = 23.1/30.1 (♂/♀)	≥2.3/3.0 mg/kg bw/day (♂/♀): ↓ MCV, ↑ total protein levels (not considered adverse) (♂); ≥23.1/30.1 mg/kg bw/day (♂/♀): ↑ ALP, ↑ total proteins (♂); ↑ lymphocytes and WBC, ↓ plasma cholesterol and triglycerides, ↓ absolute and relative kidney weights (♀) (all effects considered non-adverse); 118/163 mg/kg bw/day (♂/♀): ↓ body-weight gain, food consumption and food efficiency, thickened eyelids, ↓ Hgb, Hct and RBC, ↑ lymphocytes and WBC, ↓ cholesterol and triglycerides, ↑ plasma albumin, total protein and ALT, ↑ urine volume, ↑ relative liver weights, ↑ incidence of pale eyes, ↑ incidence of clear areas of liver hepatocytes; ↑ urinary incontinence, enlarged or discoloured testes, ↓ spermatozoa in

			the lumens of the epididymides accompanied by ↑ early, nucleated sperm precursor cells, ↑ testicular Leydig-cell hyperplasia, ↑ testicular spermatic granulomas (♂); ↓ body weight, thin appearance, distended abdomen and stained coat, ↑ plasma urea, ↓ urine pH and urinary protein levels, ↓ prothrombin time, darkened livers, ↑ bilateral and unilateral retinal atrophy, significant ↑ hemosiderin in Kupffer cells/ liver macrophages, trace urinobilinogen in urine, ↓ absolute and relative kidney weights (♀). **Neoplastic effects**: Benign Leydig-cell tumours: none observed at interim sacrifice, ↑ incidence in males (4.7%, 7.8%, 9.4% and 23.4% at 0, 2.3, 23.1 and 117.9 mg/kg bw/day, respectively Bilateral incidence of 0%, 1.6%, 0% and 9.4% at 0, 2.3, 23.1 and 117.9 mg/kg bw/day, respectively; historical controls: 12 studies from 1979–1987–mean: 6.4% (range: 0 to 19.2%). Uterine Adenocarcinoma: ↑ incidence in high-dose ♀ (1.6%, 1.6%, 0% and 4.7% at 0, 3.0, 30.1 and 162.8 mg/kg bw/day respectively; historical controls: eight studies from 1979–1985–mean: 1.85% (range: 0 to 3.8%). **Evidence of tumorigenicity in the presence of systemic toxicity.**
Developmental/Reproductive Toxicity Studies			
Multigeneration Dietary Reproduction Study–Wistar rats (3 Generation) (15♂F_0 and 30♀F_0 parents/dose)	• 0, 50, 200 or 1000 ppm (= 0, 2.5, 10 or 40 mg/kg bw/day) via the diet • 94.9% purity	**Parental**: NOAEL = 10 **Reproductive**: NOAEL = 10 **Offspring**: NOAEL = 10	**Parental**: 40 mg/kg bw/day: ↓ food consumption (F_0, F_1 and F_2) and body-weight gain (F_0, F_1 and F_2). **Reproductive**: 40 mg/kg bw/day: ↓ birth weights (F_1, F_2 and F_3). **Offspring**: 40 mg/kg bw/day: ↓ total litter weights from PNDs 5 to 22 (F_1, F_2 and F_3), ↓ pup weight gain from PNDs 5 to 22 (F_1, F_2 and F_3), ↑ absolute and relative liver weights (F_1).
Oral Teratogenicity Study–Wistar rat (24 mated ♀)	• 0, 3, 30 or 300 mg/kg bw/day by gavage (in corn oil) on gestation days 7–16 (the day of confirmation of mating was defined as GD 1), dams killed on GD 22	**Maternal**: NOAEL = 30 **Developmental**: NOAEL = 3 **Teratogenicity**: NOAEL = 30	**Maternal**: 300 mg/kg bw/day: four animals killed for humane reasons between GD 14 and 18, ↓ body weight and body-weight gain, ↓ food consumption, ↑ incidence of coat staining, piloerection, hunched posture, urinary incontinence, subdued behavior and vaginal bleeding (3/24–2 of these animals were killed

	• 96.4% purity		between GD 14 and 18), ↑ total litter resorptions (5 rats: 2 that died and three surviving to termination), ↓ number of pregnant females with live fetuses in utero at termination, ↓ number of live fetuses, ↑ in early post-implantation loss (excluding the total resorptions detected at term), ↓ gravid uterus weights (excluding the total resorptions detected at term). **Developmental**: ≥30 mg/kg bw/day: ↓ ossification of 1st cervical vertebrae and odontoid, ↑ pesticide score; 300 mg/kg bw/day: ↑ post-implantation intrauterine deaths, ↓ mean number of live fetuses, ↓ fetal size and litter weights, ↑ incidence of major defects of the vertebral centra, edema, additional major abnormalities (cleft lip and palate, bilateral curvature of the radius and ulna) (2 fetuses from different litters), pale spleens, ↑ incidence of a severe reduction in ossification, ↑ incidence of fetuses with unossified 2nd cervical centrum, ↑ incidence of fetuses with 14th ribs, ↑ proportion of fetuses with unossified odontoid, ↑ scores for manus reflecting reduced ossification. All high-dose fetuses showed at least one major or minor skeletal defect. **Teratogenic at a level causing severe maternal toxicity.**
Oral Teratogenicity Study–Wistar rat (24 pregnant ♀)	• 0, 0.5, 1, 3 or 200 mg/kg bw/day by gavage (in corn oil) on gestation days 7–16 (the day of confirmation of mating was defined as GD 1), dams killed on GD 22 • 96.4% purity	**Maternal:** NOAEL = 3 **Developmental:** NOAEL = 3 **Teratogenicity:** NOAEL = 3	**Maternal:** 200 mg/kg bw/day: ↑ mortalities (4 animals died or were killed in extremis between GD 14 and 17 with changes in the GI tract observed at necropsy), ↑ incidence of piloerection, urinary incontinence, hunched posture, thin appearance and vaginal bleeding (2 rats), ↓ body weight and body-weight gain, ↓ food consumption, ↓ gravid uterus weights. **Developmental**: 200 mg/kg bw/day: ↑ late intra-uterine deaths (4/20 females with a total of nine late ntra-uterine deaths compared to 2/23 females with a total of two late intra-uterine deaths in controls), ↓ mean fetal and litter weights, fused or misshapen vertebral centra, exencephaly, cebocephaly, ↑ incidence of minor skeletal defects and skeletal variants (indicating a

			general reduction in ossification), ↓ ossification, ↓ kinked or dilated ureters consistent with retarded development. **Teratogenic at a level causing severe maternal toxicity.**
Oral Teratogenicity Study–New Zealand White rabbits (18♀/dose)	• 0, 2.5, 20 or 100 mg/kg bw/day by gavage (in corn oil) on gestation days 7–19 (the day of insemination was designated as GD 1), dams killed on GD 30 • 97.8% purity	**Maternal**: NOAEL = 20 **Develop-mental**: NOAEL = 20 **Teratogenicity**: NOAEL = 20	**Maternal**: 100 mg/kg bw/day: nine mortalities (8 sacrificed following abortion, 1 killed in extremis on GD 18; most decedents had effects in the GI tract including hemorrhage in the stomach), ↓ body weight and food consumption, ↓ mean number of implantations (due to ↑ late intra-uterine deaths), ↓ mean number of live fetuses and mean litter weight, ↑ mean fetal weights. **Developmental**: 100 mg/kg bw/day: ↑ post-implantation losses, ↑ late intra-uterine deaths, ↓ mean number of live fetuses, ↓ mean litter weight (due to ↓ number of live fetuses), ↑ mean fetal weights, 2 head malformations in fetuses from different litters, exencephaly and cebocephaly (interparietal and occipital bones not ossified), ↑ incidence of normal length extra 13th ribs. **Teratogenic at a level causing severe maternal toxicity.**
Genotoxicity Studies			
In vitro, Ames Test (reverse mutation assay) • *S. typhimurium*	• 0, 1.6, 8.0, 40, 200, 1000 or 5000 µg/plate (in DMSO) ± activation • 94.9–95% purity	**Negative (in two studies).**	
In vitro, Mouse Lymphoma TK +/- Forward Mutation Assay • L5178Y cells	• 0, 25, 50, 100, 200 or 400 µg/ml for two hours (in DMSO) ± activation • 97.8% purity	**Negative.**	
In vitro, Cytogenicity Assay • human lymphocytes (two donors–1♂and 1♀)	• 25, 125 or 250 µg/ml (in DMSO) ± activation • 97.8% purity	**Negative.**	
In vivo, Micronucleus Assay	• 0, 300 or 480 mg/kg bw (in corn oil) by a single intraperitoneal	**Negative.**	

C57BL/6J mice (5/sex/dose/time point)	injection • 97.8% purity	
In vivo, Unscheduled DNA Synthesis Assay Male Wistar rats (5/dose/time point)	• 250, 500 and 1000 mg/kg bw (in corn oil) orally • 97.8% purity	**Negative.**
Special Studies		
3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) and 3,5-diethoxycarbonyl-4-ethyl-1,4-dihydro-2,6-dimethyl pyridine (E-DDC) used in some studies as positive control for porphyria.		
14-day Species Comparison Feeding Study– Sprague-Dawley rats, C57BL/10 CD-1 mice, Syrian hamsters and Dunkin Hartley guinea pigs (5♂/group)	• Rats, mice and hamsters: 0, 50 or 500 ppm (rats: 0, 6.4 and 61 mg/kg bw/day; mice: 0, 9.7 and 108 mg/kg bw/day; hamsters: 0, 6.0 and 57 mg/kg bw/day) via the diet for 14 days, animals killed on day 15 • Guinea pigs: 0, 100 or 1000 ppm (0, 5.5 and 54 mg/kg bw/day) via the diet for 14 days, animals killed on day 15 • 92.4% purity	***Rats***: ≥6.4 mg/kg bw/day: ↓ body-weight gain, ↓ food consumption. *no effect on hepatic cytochrome P-450 or porphyrin concentrations. ***Hamsters***: no signs of toxicity or mortalities. *no effect on hepatic cytochrome P-450 or porphyrin concentrations in both rats and hamsters. ***Mice***: ≥9.7 mg/kg bw/day: ↑ ALP, ALT and cholesterol, marked ↑ in hepatic porphyrin accumulation, marked ↓ in cytochrome P-450, ↑ absolute and relative liver weights, dark discoloured livers, enlarged liver, brown, birefringent pigment deposits distributed throughout bile ducts, Kupffer cells and hepatocytes accompanied by biliary hyperplasia, biliary fibrosis, portal inflammation and hepatocyte necrosis; 108 mg/kg bw/day: hunched, ↓ body-weight gain, ↓ food consumption, enlarged liver, ↑ in hepatocyte mitotic rate. ***Guinea pigs***: ≥5.5 mg/kg bw/day: ↓ food consumption, ↑ in cytochrome P-450; 54 mg/kg bw/day: thin appearance, ↓ body-weight gain, ↑ cholesterol, slight ↑ in hepatic porphyrin levels (histopathological and fluorescence examination of the livers produced no significant findings).
Mechanism of tralkoxydim-induced hepatic cholestasis– Sprague-Dawley rats and CD-1 mice (Per timepoint: *i*:12 mice/group, *ii*: 3 mice/group, *iii*: 15 mice/group and 15 rats/group,	• *i*: Mice: single oral dose of 0, 10 or 100 mg/kg bw, 4, 8, 12 and 24 hour sacrifice • *ii*: Mice: single oral dose of 0, 0.05, 0.1, 0.5, 1, 2, 5, 10 or 25 mg/kg bw and 0, 10, 25, 50, 100, 200, 400 or 750 mg/kg bw, 24 hour sacrifice	*i*: Mice: marked ↑ in total porphyrin content of the liver with 10 and 100 mg/kg bw (4 hours after dosing, markedly ↑ by 24 hours). *ii*: Mice: ↑ in total porphyrin content of the liver ≥2 mg/kg bw, a maximal response of 100 fold ↑ at doses of 200 to 750 mg/kg bw. The NOEL was 1 mg/kg bw. *iii*: Mice: ↑ in total porphyrin content of the liver with daily dosing at 10 and 100 mg/kg bw over a 4 day period. The NOEL was 0.5 mg/kg bw in mice. Rats: none of the doses evoked a response.

iv: 3 mice and 3 rats/group, *v*: 12 mice/group)	• *iii*: Mice and Rats: repeated daily oral doses of 0, 0.5, 10 or 100 mg/kg bw, 1, 2, 3 and 4 day sacrifice • *iv*: Mice and Rats: single oral dose of 0, 10, 25, 50, 100, 200, 400 or 750 mg/kg bw, 4 hour sacrifice • v: Mice: single oral dose of 0 or 100 mg/kg bw, 1, 2, 3 and 4 hour sacrifice • following sacrifice total hepatic porphyrin levels (i, ii, iii and v), ALAS (iv and v) and ferrochelatase (iv and v) activities were determined • vehicle–arachis oil • >95% purity	*iv*: Mice: hepatic ALAS activity was ↑ at all doses; at ≥100 mg/kg bw the ↑ was ~17X control levels. At all doses tested, mitochondrial ferrochelatase activity was ↓ to 20% of control levels. Rats: no ↑ in liver ALAS activity up to 200 mg/kg bw. At 400 and 750 mg/kg bw there was a small 2X ↑. There were no changes in ferrochelatase activity in rats tested up to 750 mg/kg bw and no changes in total liver porphyrin content 24 hours after a single oral dose up to 750 mg/kg bw. *v*: Mice: ↓ hepatic ferrochelatase activity, ↑ ALAS activity and ↑ porphyrin accumulation within 1 hour of oral dosing with values for ALAS activity ↑ up to 3 hours after dosing and total porphyrin was still increasing after 4 hours. *Tralkoxydim appears to be a fast acting and potent porphyrinogenic agent in mice, but not in rats.
Identification of an inhibitor of ferrochelatase in the livers of CD-1 mice (8♂/group)	• *i*: Extraction of inhibitory porphyrins: single i.p. injection of ^{14}C ALA, after 2 hours given single oral dose of 0, 50 or 200 mg/kg bw (in arachis oil) or 200 mg/kg DDC, sacrificed 17 hours later • *ii*: Porphyrin inhibitor obtained and purified: single oral dose of 50 mg/kg bw given to each mouse, sacrificed 4 hours later • *iii*: Ferrochelatase inhibitor and mitochondrial ferrochelatase: single oral dose of 100 mg/kg bw (in arachis oil),	The absorption spectrum of a radioactive peak detected by chromatography from liver extracts of tralkoxydim or DDC treated mice indicated the presence of an N-substituted porphyrin and was identified as N-methyl protoporphyrin IX. Proton NMR revealed the presence of only two out of four possible N-methyl isomers, indicating regioselectivity in the formation of the N-methyl protoporphyrin IX. This in turn indicates that the formation of the N-methyl compound is enzymic. N-methyl protoporphyrin IX was detected in the liver within 1 hour of dosing and increased with time. Ferrochelatase activity was consistently decreased. Male mice given single doses of tralkoxydim had concentrations of N-methyl protoporphyrin IX in the liver which peaked at 25 mg/kg bw and remained at a constant concentration at the higher dose levels.

	sacrificed 0, 1, 2, 3 and 4 hours after dosing • *iv*: Ferrochelatase inhibitor: 8 groups given single oral dose of 0, 2, 25, 50, 100, 250 or 500 mg/kg bw, sacrificed 4 hours after dosing • >95% purity	
Origin of N-methyl protoporphyrin IX in the liver of CD-1 mice (*i*: 20♂/group, *ii*:3-4♂/group)	• *i*: 50 mg/kg bw orally by gavage of ^{14}C-mesityl, ^{14}C-ethoxyimine or ^{14}C-ethyl tralkoxydim, sacrificed 4 hours after dosing. N-methyl protoporphyrin IX was extracted and extensively purified • *ii*: single oral dose of structural analogues (ethoxyimine series, C-ethyl series, tralkoxydim oxazole and tralkoxydim isoxazole) or tralkoxydim: 10, 100 or 500 mg/kg bw (in arachis oil), sacrificed 24 hours after dosing, liver homogenates prepared • vehicle: arachis oil • >95% purity	A significant amount of ^{14}C-radiolabel was found only in mice treated with ^{14}C-ethyl tralkoxydim. This indicates that the C-ethyl moiety of tralkoxydim is integral in forming N-methyl protoporphyrin IX in substantial amounts in mice. Administration of the ethoxyimine series showed a range of measurable porphyrinogenic activities and corresponding ferrochelatase inhibition with the O-methyl derivative being weakest and O-propyl being nearly comparable to tralkoxydim in porphyrinogenicity. C-alkyl alterations did not inhibit ferrochelatase or induce porphyria unlike tralkoxydim. The oxazole series lacked porphyrogenic activity. Formation of N-methyl protoporphyrin IX likely arises by direct alkylation rather than by stimulation of an endogenous pathway. The oxime structure may be required for the methyl group transfer to the protoporphyrin IX.
Potential of tralkoxydim to induce hepatic porphyrin in Sprague-Dawley rats (i *and iii*: 3♂/dose, *ii*: 20♂/dose)	• *i*: 0, 0.5, 10 or 100 mg/kg bw/day by gavage for 4 days • *ii*: 0 or 2500 ppm (250 mg/kg bw/day) via the diet for 6 months • *iii*: 0.17 μmol/kg bw 5-amino [4- ^{14}C] laevulinic acid, gavaged two hours	i. Total hepatic porphyrin contents, ferrochelatase activities, hepatic cytochrome P-450 content, liver ECOD and EROD activities were unaltered by treatment. ii. Ferrochelatase activities, total porphyria contents and liver cytochrome P-450 content were unaltered by treatment. Liver microsomal ECOD and EROD activities were increased. iii. Chromatography of liver extracts identified major peaks of (one) heme (all rats) and (two) a second peak, which was found only in rats dosed with DDC. The eluate associated with the second peak of the rat liver homogenate had marked inhibitory influence on mouse and rat liver mitochondrial ferrochelatase with DDC only.

	later with 0, 50 or 200 mg/kg bw tralkoxydim or 200 mg/kg bw DDC (positive control), animals killed 17 hours later • vehicle: arachis oil • >95% purity	
Potential of tralkoxydim to induce hepatic porphyria in male Syrian hamsters (2–3♂/group)	• single oral dose of 10 to 750 mg/kg bw or as multiple oral daily doses of 0.5, 10 or 100 mg/kg bw for 4 consecutive days • 0.17 μmol/kg bw 5-amino [4-^{14}C] laevulinic acid i.p. then gavaged two hours later with 0, 50 or 200 mg/kg bw tralkoxydim or 200 mg/kg bw DDC, animals killed 17 hours later • vehicle: arachis oil >95% purity	***Single dose***: ≥400 mg/kg bw: ↑ hepatic 5-aminolevulinic acid synthetase (ALAS) activity (small elevation compared to that reported for mice; similar to the marginal ↑ indicated for rats); 750 mg/kg bw: small but significant ↑ in total liver porphyrin. No effect on hepatic ferrochelatase activity. ***Multiple dose***: ≥100 mg/kg bw/day: ↑ in cytochrome P-450 content, ECOD and EROD activity in hepatic microsomal fractions. No effect on hepatic ferrochelatase activity. Chromatography of liver extracts revealed two distinct peaks of radioactivity: peak A corresponds with heme (present in all animals) and peak B with N-methyl protoporphyrin IX. The latter peak was present in positive controls and to a very small extent in high-dose animals. Inhibition of mouse liver ferrochelatase was clearly evident in the liver from DDC-dosed hamsters. Inhibition of mouse liver ferrochelatase was evident from liver eluate from the peak B region of tralkoxydim treated hamsters.
Induction of porphyria in in vitro primary hepatocyte cultures of Sprague-Dawley rats and CD-1 mice	• porphyrinogenic test chemicals (tralkoxydim, DDC and E-DDC) • 0, 2.5, 10, 25, 50, 100, 250 and 500 μM • >97% purity	**Mouse hepatocytes**: Marked ↑ in concentration of total porphyrin when cultured hepatocytes were exposed for 4 days. Degree of porphyrin accumulation was not sustained over the 4 day exposure period with the production of porphyrin declining towards the end of the culture period. At maximal porphyrinogenic concentrations, protoporphyrin accounted for ~70% of total porphyrin accumulating after exposure to tralkoxydim and ~85% after exposure to E-DDC and DDC. The remainder was mainly coproporphyrin and penta-carboxylporphyrin. Mitochondrial ferrochelatase activity was considerably inhibited with all; tralkoxydim appeared to be least potent with a reduction in inhibition within 24 hours in culture. **Rat hepatocytes**: Only DDC and E-DDC caused accumulation of porphyrin (mainly protoporphyrin with some coproporphyrin) and inhibition of mitochondrial ferrochelatase activity over 4 days. Tralkoxydim showed no such effects.

Induction of Porphyria in Primary Cultures of Human Hepatocytes (4♂, normal healthy liver tissue with ages ranging from 8–35 years, mean age 15 years)	• hepatocytes maintained for 3 or 4 days • 0, 10, 25, 50, 100, 250 and 500 μM tralkoxydim, 5–100 μM DDC or E-DDC • ALA added at concentrations of 0.01–1,000 μM, serve as an indicator of the cell's ability to produce porphyrin • vehicle: DMSO •>97% purity	*Highest concentrations of tralkoxydim (500 μM), DDC (100 μM) and E-DDC (100 μM) were mildly cytotoxic (loss of cells and monolayer structure). *Effects on ferrochelatase activity*: No inhibition of ferrochelatase activity was noted with tralkoxydim (10–250 μM). Exposure to DDC (5–50 μM) or E-DDC (5–50 μM) resulted in marked inhibition of ferrochelatase activity. *Effects on porphyrin accumulation*: Following exposure to DDC or E-DDC (both at 5–50 μM), occasional small non-dose related increases in total porphyrin concentration were noted. Similar sporadic increases were noted in human hepatocytes exposed to tralkoxydim (10–250 μM). These minor effects were deemed of no significance in terms of a porphyrinogenic response. *Effects of ALA addition*: ALA is an intermediate in heme biosynthesis and is the product of ALA synthetase which is the first and rate-limiting enzyme in this pathway. Consequently, addition of ALA to cells bypasses this step and results in porphyrin and heme synthesis. Thus the addition of ALA to primary hepatocytes in culture can be used as an indicator of the cells ability to produce heme/porphyrins by this pathway. The addition of ALA to human hepatocytes (0.01 to 1,000 μM) resulted in porphyrin accumulation. This confirmed that the heme biosynthetic pathway was functional in the human hepatocytes in culture and could respond to the normal stimulus of elevated ALA. From this study it can be concluded that tralkoxydim did not cause any porphyrinogenic responses in cultured human hepatocytes. Data from this study indicate that it is unlikely that porphyria would occur in vivo in humans after exposure to tralkoxydim.
Hepatotoxic effects in small wild mammals (deer mouse, white-footed mouse and meadow vole) versus laboratory mice (#/sex/species N/S)	• 100 mg/kg bw tralkoxydim or unspecified dose of DDC in deer mouse, white-footed mouse, meadow vole or Swiss laboratory •mice–known to produce liver porphyria in response to tralkoxydim • Purity N/S	Laboratory mice had significant increases in protoporphyrin levels with DDC and tralkoxydim. None of the wild species showed treatment-related responses to tralkoxydim and only the white-footed mouse showed increases in protoporphyrin with DDC. Considered supplemental

14-day Oral Toxicity Study–sexually mature Marmosets (*Callithrix jacchus*) (3/sex/dose)	• 0, 10 or 100 mg/kg bw/day (in corn oil) by gavage for 14 days • 92.4% purity	≥10 mg/kg bw/day: marginally ↓ body-weight gain (body weight loss), ↑ adrenal weights; 100 mg/kg bw/day: vomiting observed post-dosing (1♂ and 1♀); ↓ food consumption (♂); ↑ relative liver weight (♀). There was no evidence of hepatotoxicity or porphyrin accumulation in the study. No microscopic findings in the adrenal of either gender. Considered supplemental

Appendix IIIB Toxicology Endpoints for Health Risk Assessment for Tralkoxydim

EXPOSURE SCENARIO	ENDPOINT	STUDY	DOSE (mg/kg bw/day)	CAF or MOE[a]
Acute Dietary	♀ 13–49 years: ↑ post-implantation losses and late intra-uterine deaths, ↓ litter weight and number of live fetuses, two head malformations and ↑ incidence of normal length extra 13th ribs	An oral (gavage) developmental toxicity study in the rabbit	20	300
	ARfD ♀13–49 years = 0.067 mg/kg bw			
	General population: maternal toxicity with weight loss detected after one day of exposure	An oral (gavage) developmental toxicity study in the rabbit	20	100
	ARfD general population = 0.2 mg/kg bw			
Chronic Dietary	Hepatotoxicity and an effect on the adrenals in both males and females	An oral (capsule) 12-month toxicity study in the dog	0.5	100
	ADI = 0.005 mg/kg bw/day			
Short- and Intermediate-term Dermal and Inhalation[b]	Reduced ossification	Two oral (gavage) developmental toxicity studies in the rat	3	100
Cancer Risk Assessment	An adjusted Q_1^* value of 1.08×10^{-2} (mg/kg bw/day)$^{-1}$ from the two year chronic toxicity/carcinogenicity study in rats based on the increased incidence of benign Leydig-cell tumours in males.			
Aggregate Risk Assessment–Food and Drinking Water	The most relevant studies are those selected for the Acute Reference Dose and the Acceptable Daily Intake for acute and repeated exposure scenarios, respectively.			

[a] CAF (composite assessment factor) refers to total of uncertainty and *Pesticide Control Products Act* factors for dietary assessments, MOE refers to desired margin of exposure for occupational or residential assessments

[b] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) should be used in route-to-route extrapolation

Appendix IV Occupational Exposure Risk Estimates for Tralkoxydim

Table A Commercial Mixer/Loader/Applicator Non-Cancer Exposure and Risk Assessment

Scenario	Form	Application Equipment	Data Source	Rate (kg a.i./ha)	ATPD (ha)	Kg a.i. Handled per Day	Unit Exposure (µg/kg a.i.)		Exposure (µg/kg/day)[b]		MOE[c]		
							Total		Daily		Dermal	Inhalation	Comb[d]
							Dermal	Inhalation	Dermal	Inhalation	Target=100		
Personal Protective Equipement: M/L: coveralls over long sleeved shirt, long pants, chemical resistant gloves; A: long sleeved shirt, long pants													
Cereal grains, forage grasses[a]	EC	Groundboom	PHED	0.2	100	20	65.75	2.56	5.64	0.73	532	4100	471
		Groundboom (custom)			300	60	65.75	2.56	16.91	2.19	177	1370	157
		Aerial (M/L)			400	80	32.77	1.6	11.24	1.83	267	1640	230
		Aerial (A)			400	80	9.66	0.07	3.31	0.08	906	37500	884

Form = formulation; EC = emulsifiable concentrate; ATPD = area treated per day; MOE = margin of exposure;
Comb = combined MOE; M/L = mixing/loading; A = application; PHED = Pesticide Handler Exposure Database

a Cereal grains: Wheat (spring, winter, durum), barley, triticale, rye (spring, winter); Forage grasses: timothy (for seed production, established), wheat grass (intermediate, crested, northern, western, slender), creeping red fescue, brom grass (meadow, smooth). Also covers off some minor use crops.

b Where exposure (µg/kg/day) = (unit exposure × kg a.i. handled per day)/70 kg bw. A dermal absorption value of 30% was used in the dermal exposure calculation.

c Dermal and inhalation MOEs are based on an oral NOAEL of 3 mg/kg bw/day, target is 100.

d Calculated using the following equation: Combined MOE = 1/[1/dermal MOE + 1/inhalation MOE].

Table B Commercial Mixer/Loader/Applicator Cancer Exposure and Risk Assessment

Scenario	Form	Application Equipment	Data Source	Rate (kg a.i./ha)	ATPD (ha)	Kg a.i. Handled per Day	Frequency (days/year)	ADD[b] (µg/kg/day)[c]		LADD[d] (mg/kg bw/day)	Cancer Risk[e]
								Dermal	Inhalation		
Personal Protective Equipment: M/L: coveralls over long sleeved shirt, long pants, chemical resistant gloves. A: long sleeved shirt, long pants											
Cereal grains, forage grasses[a]	EC	Groundboom	PHED	0.2	100	20	15	5.64	0.73	1.40 E-04	1.51 E-06
		Groundboom (custom)			300	60	30	16.91	2.19	8.37 E-04	9.04 E-06
		Aerial (M/L)			400	80	15	11.24	1.83	2.86 E-04	3.09 E-06
		Aerial (A)			400	80	15	3.31	0.08	7.43 E-05	8.03 E-07
		Aerial (M/L) (custom)			400	80	30	11.24	1.83	5.73 E-04	6.18 E-06
		Aerial (A) (custom)			400	80	30	3.31	0.08	1.49 E-04	1.61 E-06

Shaded cells indicate risks that are less than 1×10^{-5}.

Form = formulation; EC = emulsifiable concentrate; ATPD = area treated per day; M/L = mixing/loading; A = application, PHED = Pesticide Handler Exposure Database

[a] Cereal grains: Wheat (spring, winter, durum), barley, triticale, rye (spring, winter); Forage grasses: timothy (for seed production, established), wheat grass (intermediate, crested, northern, western, slender), creeping red fescue, brom grass (meadow, smooth). Also covers off some minor use crops.

[b] ADD= absorbed daily dose. Values are from Table A (Non-cancer).

[c] Where exposure (µg/kg/day) = (unit exposure × kg a.i. handled per day)/70 kg bw. A dermal absorption value of 30% was incorporated into the dermal exposure values from Table A

[d] LADD= lifetime average daily dose. LADD= (ADD × treatment frequency × working duration (40 years))/(365 days/year × life expectancy (75 years)).

Table C Commercial Non-Cancer Postapplication Exposure

Activity	Transfer Coefficient (cm^2/hr)	DFR[b] ($\mu g/cm^2$)	Dermal Exposure[c] (µg/kg bw/day)	MOE[d] (Day 0)	REI[e]
Workers in Cereal Crops and Forage Grasses [a]				**Target: 100**	
Scouting, irrigation (full foliage/height)	1500	0.4	20.57	146	12 hours
Scouting, irrigation (min foliage/height)	100	0.4	1.37	2190	12 hours

[a] Cereal grains: Wheat (spring, winter, durum), barley, triticale, rye (spring, winter); Forage grasses: timothy (for seed production, established), wheat grass (intermediate, crested, northern, western, slender), creeping red fescue, brom grass (meadow, smooth). Also covers off minor use crops as listed in Table 1.1.

[b] DFR = dislodgeable foliar residue. DFR value was determined using default peak DFR value of 20% of the application rate.

[c] Exposure = DFR × TC × duration (8 hours) × DA (30%) / body weight (70 kg).

[d] Based on worker short-term oral NOAEL of 3 mg/kg bw/day and target MOE of 100

[e] REI = restricted-entry interval. 12 hours is the minim REI.

Table D Commercial Cancer Postapplication Exposure

Activity	Transfer Coefficient (cm^2/hr)	DFR[b] ($\mu g/cm^2$)	Frequency (days/year)	ADD[c] (µg/kg bw/day)	LADD[d]	Cancer Risk[e]
Workers in Cereal Crops and Forage Grasses [a]						
Scouting, irrigation (full foliage/height)	1500	0.4	30	20.57	9.02 E-04	9.74 E-06
Scouting, irrigation (min foliage/height)	100	0.4	30	1.37	6.01 E-05	6.49 E-07

[a] Cereal grains: Wheat (spring, winter, durum), barley, triticale, rye (spring, winter); Forage grasses: timothy (for seed production, established), wheat grass (intermediate, crested, northern, western, slender), creeping red fescue, brom grass (meadow, smooth). Also covers off minor use crops as listed in Table 1.1.

[b] DFR = dislodgeable foliar residue. DFR value was determined using default peak DFR value of 20% of the application rate.

[c] ADD = absorbed daily dose. Values are from Table C (Non-cancer). A dermal absorption value of 30% was incorporated into these dermal exposure values.

[d] LADD = lifetime average daily dose. LADD= (ADD × treatment frequency x working duration (40 years))/(365 days/year × life expectancy (75 years)).

[e] Risk = LADD × Q_1^* (1.08×10^{-2})

Appendix V Dietary Exposure and Risk Estimates for Tralkoxydim

Table 1 Acute Dietary Exposure and Risk for Tralkoxydim

Population Groups	Food		Food and Water	
	Exposure[1] (mg/kg bw/day)	% ARfD[2]	Exposure[1] (mg/kg bw/day)	% ARfD[2]
General Population[3]	NA	NA	NA	NA
All Infants (<1 year old)	0.0001	<1	0.004	2
Children 1–2 years old	0.0003	<1	0.003	<1
Children 3–5 years old	0.0002	<1	0.002	1
Children 6–12 years old	0.0002	<1	0.001	<1
Males 13–19 years old	0.0001	<1	0.001	<1
Females 13–49 years old	0.0001	<1	0.001	1
Males 20–49 years old	0.0001	<1	0.001	<1
Adults 50+ years old	0.0001	<1	0.001	<1

NA = not applicable

1 95th percentile of exposure

2 ARfD for all population groups (except females 13–49) was based on a NOAEL of 20 mg/kg bw/day from a rabbit developmental toxicity study, composite assessment factor of 100 was applied.
For females 13–49, ARfD based on NOAEL of 20 mg/kg bw/day from the same rabbit developmental toxicity study, composite assessment factor of 300 was applied.

3 The risk estimate could not be determined for the general population as a separate ARfDs was selected for females aged 13–49 years and the other population groups.

Table 2 Chronic Non-Cancer Dietary Exposure and Risk for Tralkoxydim

Population Groups	Food		Food and Water	
	Exposure (mg/kg bw/day)	% ADI[1]	Exposure (mg/kg bw/day)	% ADI[1]
General Population	0.000023	<1	0.00003	<1
All Infants (<1 year old)	0.000014	<1	0.00001	<1
Children 1–2 years old	0.000054	1	0.00006	1
Children 3–5 years old	0.000051	1	0.00006	1
Children 6–12 years old	0.000035	<1	0.00004	<1
Youth 13–19 years old	0.000023	<1	0.00003	<1
Adults 20–49 years old	0.000020	<1	0.00003	<1
Females 13–49 years old	0.000017	<1	0.00002	<1
Adults 50+ years old	0.000017	<1	0.00002	<1

[1] ADI for all populations based on NOAEL of 0.5 mg/kg bw/day from a 12 month dog toxicity study, composite assessment factor of 100 was used.

Table 3 Chronic Cancer Dietary Exposure and Risk for Tralkoxydim

Population Group	Lifetime Cancer Risk[1]	
	Food	Food and Water
General Population	2.5×10^{-7}	3.2×10^{-7}

[1] Cancer Unit Risk (Q_1^*) based on bioassay data from a two year chronic toxicity/ carcinogenicity study in rats, Q_1^* value of 1.08×10^{-2} $(mg/kg\ bw/day)^{-1}$ was used.

Appendix VI Food Residue Chemistry Summary

1.1 Metabolism

Plant Metabolism

Three wheat metabolism studies are on file with the PMRA. In the studies, radio-labeled tralkoxydim was applied to wheat at 1.3 to 1.75 times label rates. The pre-harvest intervals (PHIs) ranged from 16 to 100 days for forage and straw samples and 92 to 100 days for grain samples. Tralkoxydim equivalent residues were primarily distributed in straw and forage parts of the plant, as residue concentrations in grain samples (0.005–0.02 ppm) were at least 5x lower than concentrations in straw and forage samples (0.10–2.06 ppm). The major residue component found in forage and straw was 2,6-dimethyl-4-(2-ethyl-4,5,6,7-tetrahydro-benzoxazol-4-one) benzyl alcohol, which accounted for approximately 10–20% of the total radioactive residue (TRR) in those matrices. Several other metabolites (at least five) were also identified at amounts that were generally below 10% of the TRR. The parent, tralkoxydim was not detected in any of the straw and forage samples, indicating that it was extensively metabolized. The metabolic profile of tralkoxydim in grain could not be characterized in any of the studies, due to low total residue content. Based on the data available, residues of tralkoxydim and its related metabolites are expected to occur in low amounts in cereal grains. Thus, the residue definition in cereal commodities is the parent, tralkoxydim.

1.1.2 Animal Metabolism

Adequate goat and hen metabolism studies were available on file to determine the nature of the residue in livestock.

Two goat metabolism studies were submitted to the PMRA. One of the studies was conducted to examine the metabolic profile of tralkoxydim while the other study was conducted to examine the metabolism of the major plant tralkoxydim metabolite, 2,6-dimethyl-4-(2-ethyl-4,5,6,7-tetrahydro-benzoxazol-4-one) benzyl alcohol or U5, which was found in significant amounts in wheat straw and forage.

In the tralkoxydim goat metabolism study, two lactating goats were dosed at a nominal rate of 10 mg a.i./kg feed for seven consecutive days. The majority of the administered dose was found in excrements (urine, faeces, cage wash) accounting for 52.6–58.5% of the total dose. Residue contents found in tissue and milk samples were <2.3% of the applied dose. The unmetabolized form of tralkoxydim accounted for 52.7–91.3% of the TRR in tissues (fat, liver, kidney, muscle) and milk and 13.7% of the TRR in urine. The only metabolite found at significant amounts was tralkoxydim acid (4-(2-[1-ethoxydiminiopropyl]-3-hydroxy-2cycloexen-1one-5-yl)-3,5-dimethylbenzoic acid), which accounted for 39.7%, 11.2% and 2.5% of the TRR in the urine, kidney and liver, respectively.

A similar experimental protocol was followed in the U5 goat metabolism study, again two lactating goats were dosed at a nominal rate of 10 mg a.i./kg feed for seven consecutive days. The majority of the administered dose was excreted via urine and faeces accounting for 86–94% of the total dose. Residue content found in tissue and milk sample were negligible and accounted for ≤0.1 % of the applied dose. Three significant metabolites were identified in urine accounting for 93% of the TRR; 2,6-dimethyl-4-(2-ethyl-4, 5, 6, 7-tetrahydrobenzoxazol-4-one) benzoic acid (51% TRR), cis-2-ethyl-4-hydroxy-4,5,6,7-tetrahydro-6-(4-carboxy-2,6-dimethylphenyl) benzoxazole (15% TRR), and trans-2-ethyl-4-hydroxy-4,5,6,7-tetrahydro-6-(4-carboxy-2,6-dimethylphenyl) benzoxazole (27% TRR). These metabolites combined also accounted for the majority of TRR in kidney (65.2% TRR), liver (46.5% TRR), and milk (76.6% TRR). The parent compound was not found in any of the milk, urine and tissues (kidney, liver) samples analyzed.

A single poultry metabolism study was submitted to the PMRA. In the study, tralkoxydim was orally administered to hens at a nominal rate of 10 mg a.i./kg feed for 10 consecutive days. The majority of the residues were found in faeces and cage washing, which accounted for 73–97% of the applied dose. Total residue content in tissues and eggs was negligible and accounted for 0.5–1.3% of the applied dose. The TRR in tissues and egg samples comprised principally of two compounds, tralkoxydim and an acid metabolite, 4-(2-[1-(ethoxyimino)propyl]-3-hsydroxy-2-cyclohexen-1-one-5-yl)-3,5-dimethylebenzoic acid. Tralkoxydim accounted for 2.2–83.2% of the TRR while tralkoxydim acid accounted for 7.7–82.6% TRR in eggs, faeces and tissues.

Overall, the data indicates that tralkoxydim and its major plant metabolite U5 are extensively metabolized and excreted in animals. Minimal residues were detected in tissues, milk, and eggs of animals dosed with tralkoxydim or U5 at exaggerated rates. The major metabolic pathway appears to be conserved between species as 4-(2-[1-ethoxydiminiopropyl]-3-hydroxy-2cycloexen-1one-5-yl)-3,5-dimethylbenzoic acid, was the major metabolite identified in all test species. Since tralkoxydim residues were not detected in any treated cereal grains, straw and forage samples, tralkoxydim exposure to livestock from crop feeds is expected to be minimal. Given the results of the metabolism data, residues of tralkoxydim and its metabolites are expected to occur in very low amounts in livestock, and the residue definition and MRL for animal commodities is required. This decision is consistent with those proposed by the USEPA and European Food Safety Authority (EFSA).

1.1.3 Canadian and International MRLs

When pesticides are used on crops or when animals are fed crops treated with pesticides, residues may remain in or on the food when it is sold. The PMRA must determine the amount of residues that are likely to remain in or on the food when the pesticide is used according to label directions and poses no unacceptable risks to human health. This amount is then legally established as the maximum residue limit (MRL) under the *Pest Control Products Act*. Pesticides that do not have established MRLs on food commodities are covered by the general MRL under subsection B.15.002 (10) of the Food and Drugs Regulation of the *Food and Drugs Act* (≤0.1ppm). A summary of tralkoxydim Canadian and international MRLs are provided in Table 1. There no MRLs for tralkoxydim listed in the Codex Alimentarius.

Table 1 Tralkoxydim Canadian and International MRLs

Canadian MRL (ppm)	
Barley, Wheat	0.02
Rye, Triticale[1]	0.10
United States Tolerance (ppm)	
Barley (grain, hay), Wheat (grain, hay)	0.02
Barley (straw), Wheat (straw, forage)	0.05
European Food Safety Authority MRL (ppm)	
Wheat, Barley, Rye, Triticale, Oats	0.01

[1] Covered under Part B, Division 15, subsection B.15.002(1) of the Food and Drugs Regulation as ≤0.1 ppm

1.1.4 Residue Definition

The residue definition is used to describe the sum of the parent pesticide, its degradation products, metabolites and impurities that are of toxicological concern. All components of the residue definition will normally be included in the MRL expression of the pesticide and residue analytical methods must be developed, for all components of the residue definition.

Based on metabolism data the residue definition in cereal commodities is the parent, tralkoxydim. The residue definition for animal commodities is not required, as very low residues are expected to occur in livestock when fed with crops treated according to label directions.

Table 2 Residue Definition

PLANT	
RESIDUE DEFINITION FOR MONITORING AND MAXIMUM RESIDUE LIMIT	Tralkoxydim
RESIDUE DEFINITION FOR RISK ASSESSMENT	Tralkoxydim

1.2 Analytical Methods

1.2.1 Methods for Residue Analysis in Plants

Several High Performance Liquid Chromatography (HPLC) methods were developed to analyze tralkoxydim in cereal crops.

Based on the data available, the HPLC-MS/MS method termed "RAM 398/10" is considered to be the most appropriate method to use for enforcement purposes. The limit of quantification (LOQ) for the method was successfully validated at 0.01 ppm in wheat and a variety of other crops.

Residue Analytical Method (RAM) 398/01 (Crook SJ, 2003, PMRA #1567180. Ryan J, 2003, PMRA #1567181)

Samples are extracted by homogenisation with acetonitrile. Extracts are centrifuged and aliquots (0.1 g in 1 mL) are diluted with ultra-pure water. Samples are partitioned into dichlorormethane. A silica solid phase extraction procedure is then carried out, to facilitate further sample clean up. Final determination is by HPLC, with triple quadrupole mass spectrometric detection (HPLC-MS/MS).

The LOQ was determined to be 0.01 ppm. The method was validated and tested on a variety of crops including wheat straw/grain, orange whole fruit, tomato, oat forage and rapeseed oil. The mean recovery ranged from 74% to 102% at the 0.01 ppm and 0.1 ppm fortification levels.

RAM 99A (Earl M, Tummon OJ, 1988, PMRA # 1224324. Earl M, 1989, PMRA # 1567182. Earl M, 1991, PMRA # 1142850)

Grain samples are extracted by homogenisation with acetonitrile. The extracts are filtered through Whatman Number 1 filter paper, rinsed with acetonitrile, and evaporated to dryness. The samples are then subjected to further cleanup via adsorption chromatography (Bond Elut diol and amino column). The eluate is evaporated again and resuspended in acetonitrile prior to analysis using HPLC-UV. For straw and foliage samples, an additional liquid-liquid partitioning step is added to the acentonitrile filtrate.

The LOQ was determined to be 0.02 ppm. The method was validated and tested in barley (foliage, grain and straw), wheat (foliage, grain and straw), rye (foliage, grain and straw) and soil. Tralkoxydim residue recoveries were adequate (70–120%) for all matrices at fortification levels between 0.1–5 ppm. In addition, sufficient recovery was observed in wheat grain fortified at 0.02 and 0.05 ppm, and barley grain fortified at 0.05 ppm.

RAM 281/01 (Entwistle K, Newcombe A, 1996. PMRA #1567183)

Samples are extracted via homogenization with acetonitrile. The filtered extracts of forage and straw are subjected to liquid-liquid partition with dichloromethane and water. The organic portion is evaporated to dryness and resuspend in a 1:1 dichloromethane:hexane solution. An aliquot of the solution is subjected to clean up using Bio-Rad Bio-BeadsTM SM7 (20-mesh) column, followed by diol and amino column adsorption chromatography. The eluate is evaporated to dryness and resuspended in acetonitrile prior to quantitative determination of tralkoxydim by reverse phase HPLC-UV. Wheat grain was subjected to the same procedures except liquid-liquid partition and Bio-Rad Bio-BeadTM column clean-up portions of the protocol were not performed.

The LOQ was established at 0.02 ppm. Tralkoxydim was applied to wheat straw, grain and forage at several fortification levels ranging between 0.02–1.00 ppm. All recoveries were within the adequate range of 70 to 120%.

Independent Laboratory Validation (ILV)

RAM398/01 (Brice A, Irlam S, 2003, PMRA # 1567184)

Independent Laboratory Validation (ILV) of RAM398/01 was completed at Covance Laboratories LTD. Control samples of tomato and wheat grain were fortified with 0.01 ppm or 0.1 ppm tralkoxydim. Recoveries ranged from 87 to 102% with standard deviation of 3.4–13.6%.

Method TMJ3237B (Van Neste LA, 1994, PMRA # 1567185)

An ILV study was performed at Zeneca AG laboratories for the method "TMJ3237B". This method is listed in the USEPA's analytical method website for the detection of tralkoxydim in wheat forage, grain, hay and straw. The method LOQ is stated at 0.02 ppm. According to study procedure, samples were extracted by maceration with acetonitrile. The macerates were vacuum filtered, mixed with dichloromethane for clean-up, and evaporated to dryness under reduced pressure at 40°C. The samples are then subjected to further clean up via diol-solid phase extraction column and amino solid-phase extraction column. The eluate was evaporated and resuspended in acetonitrile prior to analysis using HPLC-UV.

The first validation run for TMJ3237B was not successful and minor changes were recommended to the method procedure. The changes included the addition of a guard column in the HPLC system and the inclusion of a gradient to the sample run. It was also suggested that the extraction process and the HPLC analysis be performed on two separate days. The second validation run included the recommended changes and was successful. Recovery was adequate (92–111%) for samples of wheat straw fortified at 0.1 ppm and 0.2 ppm. The method LOQ was not validated.

1.2.2 Methods for Residue Analysis of Food of Animal Origin

Based on data from animal metabolism studies, residues for tralkoxydim are expected to occur in very low amounts in animal tissues, milks, and eggs when fed with crops treated and harvested according to label directions. Thus the development of analytical methods to detect tralkoxydim in animals is not required.

1.2.3 Multi-Residue Analytical Method

Tralkoxydim is not listed in the Canadian Food Inspection Agency's (CFIA's) Pesticide Multi-Residue Analytical Methods Manual.The registrant has submitted a study to the PMRA (Gillard DF, 1991, PMRA# 1567186), which evaluated multiresidue methods from the United States Food and Drug Administration (FDA) Pesticide Analytical Manual (PAM) Volume I. None of the methods in Pesticide Analytical Manual Volume I demonstrated sufficient recovery and therefore are not suitable for the quantitative analysis of tralkoxydim.

1.3 Food Residues

1.3.1 Storage Stability

Storage stability data on file is limited. The PMRA requests the registrant to submit contemporary studies in accordance with Regulatory Directive DIR98-02, *Residue Chemistry Guidelines*. The limitations of the current study data are outlined below.

Stability of Tralkoxydim Residues in Wheat Forage when Stored at < -15°C (Hurt AD, 1999, PMRA # 1581321)

The study examined the freezer storage stability of tralkoxydim in wheat forage samples. Treated samples of wheat straw from a 1995 United States field trial (Jones SD, Roper E , 1996. PMRA # 1581322) were collected and stored for 12 months. The residues from these samples were determined. The samples were subsequently put back into storage for an additional 21 months and re-analyzed. The residue data for the samples after 12 months of storage were compared to the residue data after the additional 21 months of storage. No significant decrease in tralkoxydim residue level was observed.

The experimental design for this study is not acceptable. According to the 1995 United States field trial study, forage samples were stored for approximately 12 months (370–376 days) before residues were analyzed. Thus, the initial residue in the samples prior to storage were not determined and the amount that may have declined between 0 to12 months was not taken into account. Essentially, the study presented freezer residue data of tralkoxydim in forage between the 12 to 33 month period of frozen storage. This data may not accurately reflect the initial residue degradation phase of tralkoxydim residue and cannot be used quantitatively or qualitatively to assess storage stability.

Storage Stability of the Residue in Frozen Grain and Straw (Earl, M, 1988. PMRA #1581320)

The study examined the freezer storage stability of tralkoxydim in grain and straw. The crop species tested was not specified. Grain and straw samples were fortified with tralkoxydim at a nominal dose of 0.1 ppm and stored at <-18°C for up to 18 months (587 days). Residues were analyzed in samples at set time intervals using analytical method RAM99A, as described in the analytical method section. Results indicated that ≥70% of residues remained in all samples after nine months of storage; however, at 12 months, residues declined to 91% in grain and 69% in straw. At 18 months, residues declined to 80% in grain and 64% in straw. The data for grain samples is not acceptable as the initial concentration of tralkoxydim was not determined and residue data on day 1 of storage was used as a surrogate instead. Residue data determined on day 1 of storage may underestimate the initial residue concentration prior to storage as significant amounts may have declined during the first day. The data from straw indicate that samples should be analysed within approximately nine months of storage (<279 days) to avoid significant loss of residues (>30%). Refer to Table 3 for details.

Overall, freezer storage stability data for tralkoxydim in plants is limited. The registrant is requested to submit an adequate storage stability study conducted on a cereal crop in both grain and straw and/or forage matrices. The study should be conducted in accordance with Regulatory Directive DIR98-02, *Residue Chemistry Guidelines*.

Table 3 Storage Stability of Tralkoxydim in Grain and Straw

Crop Part	Storage Time (Days)	Mean Residue (ppm)	Mean Residue %
Grain	0	N/A	N/A
	1	0.102	100
	37	0.09	88
	94	0.09	88
	185	0.091	89
	301	0.078	76
	367	0.093	91
	553	0.082	80
Straw	0	0.112	100
	1	0.079	71
	33	0.092	82
	98	0.085	76
	187	0.09	80
	279	0.082	73
	370	0.077	69
	578	0.072	64

N/A = not available

Freezer Storage Stability in Animals

Tralkoxydim residues are expected to occur in very low amounts in animal matrices; therefore, tralkoxydim storage stability data in animal matrices are not required.

1.3.2 Crop Residues

Wheat

Canada

A total of six trials were carried out in Manitoba, Alberta and Saskatchewan (Zone 7, 14) during 1986, 1987, and 1992. Several formulations, rates and PHIs were tested in these trials (refer to Table 4 for details). The major tralkoxydim plant metabolite U5 was also analyzed in a 1992 Canadian field trial. Residues of tralkoxydim and U5 did not exceed the method LOQ (0.02 ppm for tralkoxydim, 0.01 ppm for U5) in any treated grain samples. Similarly, residues of tralkoxydim in forage and straw were non-quantifiable (<0.02 ppm) when treated and harvested according to the label rates and PHI. Based on the data available, tralkoxydim residues in wheat are not expected to exceed the current registered MRLs of 0.02 ppm.

Table 4 Tralkoxydim Residue Data from Canadian Wheat Field Trials

Crop	Rate (g a.i./ha)	Formulation	PHI (Days)	Maximum Residue (PPM)	Analytical Method	Storage Conditions*
1986 Field Trial in Saskatchewan and Manitoba (Earl M, Laws I, 1987, PMRA # 1224273)						
Wheat Grain	0.3, 0.6	DF, EC	108	<0.02	RAM 99A	<-20°C, time not specified
1987 Field Trial in Manitoba (Cunningham SM, Earl M, 1987, PMRA # 1224274)						
Wheat Grain	0.3, 0.6	DF	75–98	<0.02	RAM 99A	<-18°C, time not specified
Wheat Forage	0.3, 0.6	DF	49–50	<0.02	RAM 99A	
Wheat Straw	0.3, 0.6	DF	83–98	<0.02	RAM 99A	
1992 Field Trial in Manitoba and Saskatchewan (Plant Metabolite U5) (Earl M, 1993, PMRA # 1149446)						
Wheat Gain	0.2, 0.25	WG	90–96	<0.01	HPLC/MS[1]	3–15 months, <-12°C
1992 Field Trial in Manitoba and Saskatchewan (Runnalls JK, 1994, PMRA #1159002)						
Wheat Grain	0.2, 0.25	WG	90–96	<0.02	RAM 99A	3–15 months, <-12°C
Wheat Forage	0.2, 0.25	WG	14–75	<0.02	RAM 99A	

EC= Emusifiable Concentrate, DF=Dry Flowable , WG=Wettable granule
[1]LOQ at 0.01 ppm, mean external standard recovery = 82%

*Note: Inadequate sample storage information was identified as a limitation in the Canadian field trial studies; samples in 1992 field trials were stored for 3–15 months (<-12°C), while 1986, 1987 studies did not provide the storage times. Storage stability data on file indicates that samples should be stored within nine months of collection to prevent the significant loss of residues (>30%); however, this data is highly uncertain as it was based on a limited study.

United States

Several United States wheat field trial studies were submitted to the PMRA. The USEPA review (1998) of these studies is considered to be acceptable by the PMRA and is provided below.

A total of 25 wheat field trials were conducted during 1994 and 1995. Three trials were conducted in 1994 in Idaho, Montana and Wyoming. At each site, a single application of tralkoxydim (40% DF) was applied at a rate of 280 g a.i./h. A single control and treated samples of forage were harvested twice from each trial, first at 27–30 days postapplication and again at 42–45 days postapplication. A single grain and straw sample was also harvested from each trial with the PHI ranging from 63–88 days. Samples were held in frozen storage for a total of 268–295 days in less than -15°C conditions prior to analysis. Residue of tralkoxydim in grain, forage, and straw samples were determined using RAM 281/01 as described in the analytical method section. The validated LOQ is 0.02 ppm. Concurrent method recoveries ranged from 74 to 111% for two control samples each of forage, grain, and straw fortified with tralkoxydim at 0.025 ppm. Tralkoxydim residues were undetectable in treated samples tested (three grain, four straw, and four forage samples).

In 1995, 20 trials were conducted on spring and winter wheat in Colorado, Illinios, Kansas, Minnesota, Mississippi, Montana, North Carolina, North Dakota, Nebraska, Okalahoma, South Dakota, Texas and Washington. Spring wheat was used at seven sites and winter wheat was used at 13 sites. At all sites, tralkoxydim (80% DF) was applied as a post-emergence application at a rate 280 g a.i./ha.

In 18 of the trials, a single control sample and duplicate treated samples of wheat forage, hay, grain and straw were collected. Forage samples were harvested 13–14 days post-treatment, while hay samples were cut 28–81 days post-treatment and were dried for an additional 2–13 days prior to sampling. Grain and straw samples were harvested at maturity, 57–119 days post-treatment.

In two of the trials (Illinois and Mississipi), which were used as residue decline studies, single treated samples of forage, hay, grain and straw were harvested at four PHIs. Forage samples from both residue decline studies were collected at 7–28 days postapplication. Hay samples were cut 22–41 days postapplication from the Illinois trial and 19–39 days postapplication from the Mississippi trial. The hay samples from both trials were dried for an additional 2–9 days prior to sampling. Wheat grain and straw samples were harvested 74–96 days postapplication from the Illinois trial and 77–98 days postapplication from the MS trial. Samples were frozen for 223–415 days prior to analysis. Residues of tralkoxydim in hay, straw and grain were determined using an LS/MS-MS method. Adequate method recoveries (70–111%) were obtained for controls samples fortified with tralkoxydim at 0.02 ppm (method LOQ). Samples were held in frozen storage for a total of 223–415 days in <-18°C conditions prior to analysis.

Residues of tralkoxydim were <0.02 ppm in/on all treated samples of grain and straw that were harvested at 57–119 days postapplication. Residues of tralkoxydim were also < 0.02 ppm in/on 42 treated hay samples harvested 19–81 days postapplication. Residues of tralkoxydim were detected at 0.13 and 0.08 ppm in/on two treated hay samples from one of the residue decline studies (Illinois), harvested at 22 and 28 days postapplication. Tralkoxydim residues ranged from 0.02 to 0.8 ppm in samples of forage harvested 13–14 days post-treatment. The majority of the samples had residues below 0.1 ppm with the exception of 4 samples from Kansas trials harvested at 14 days postapplication; 0.80 ppm, 0.70 ppm, 0.38 ppm, 0.34 ppm. The petitioner stated that abnormally high residue was due to drought conditions, which resulted in reduced plant growth.

Barley

Canada

Supervised barley fields trial studies conducted in Canada have been previously reviewed by the PMRA (1994, 2003).

A total of eight trials were carried out in Manitoba, Alberta and Saskatchewan (Zone 7, 14) during 1986, 1987 and 1992. Several formulations, rates (1–3 times label rate) and PHIs were tested in these trials (refer to Table 5 for details). The major tralkoxydim plant metabolite U5 was also analyzed in a 1992 Canadian field trial. Residues of tralkoxydim and U5 did not exceed the method LOQ (0.02 ppm for tralkoxydim, 0.01 ppm for U5) in any grain, forage and straw samples, when treated and harvested according to label direction. Based on the current data, tralkoxydim residues in wheat are not expected to exceed the current registered MRL of 0.02 ppm.

Table 5 Tralkoxydim Residue Data from Canadian Wheat Field Trials

Crop	Rate (kg a.i./ha)	Formulation	PHI (Days)	Maximum Residue (PPM)	Analytical Method	Storage Conditions*
1986 Field Trial in Saskatchewan and Manitoba (Earl M, Laws I, 1987, PMRA # 1224273)						
Barley Grain	0.3, 0.6	DF, EC	75–108	<0.02	RAM 99A	-20°C, time not specified
1987 Field Trial in Manitoba (Cunningham SM, Earl M, 1987, PMRA # 1224274)						
Barley Grain	0.3, 0.6	DF	75–98	<0.02	RAM 99A	<-18°C, time not specified
Barley Forage	0.3, 0.6	DF	45–50	<0.02	RAM 99A	
Barley Straw	0.3, 0.6	DF	83–98	<0.02	RAM 99A	
1992 Field Trial in Manitoba and Saskatchewan (Plant Metabolite U5) (Earl M, 1993, PMRA #1149446)						
Barley Grain	0.2, 0.25	WG	88–90	<0.01	HPLC/MS[1]	3–15 months, <-12°C
1992 Field Trial in Manitoba, Alberta and Saskatchewan (Runnalls JK, 1994, PMRA #1159001)						
Barley Grain	0.2, 0.25	WG	88–90	<0.02	RAM 99A	3–15 months, <-12°C
Barley Forage	0.2, 0.25	WG	8–65	<0.02	RAM 99A	
Barley Straw	0.2	WG	90	<0.02	RAM 99A	

EC= Emusifiable Concentrate, DF-Dry Flowable , WG=Wettable granule

[1] LOQ at 0.01 ppm, mean external standard recovery = 82%

* Note: Inadequate sample storage information was identified as a limitation in the Canadian field trial studies; samples in 1992 field trials were stored for 3–15 months (<-12°C), while 1986, 1987 studies did not provide the storage times. Storage stability data on file indicates that samples should be stored within nine months of collection to prevent the significant loss of residues (>30%); however, this data is highly uncertain as it was based on a limited study.

United States

Several United States barley field trial studies were also submitted to the PMRA. The USEPA review (1998) of these studies is considered to be acceptable by the PMRA and is provided below.

A total of 15 barley field trials were conducted during 1994 and 1995.Three trials were conducted in 1994 in Idaho, Montana and Wyoming. At each site, a single application of tralkoxydim (40% DF) was applied at a rate of 280 g a.i./h. A single control and treated sample of grain and straw were harvested from each trial with the PHI ranging from 62–90 days. Samples were held in frozen storage for a total of 268–295 days in less than -15°C conditions prior to analysis. Residue of tralkoxydim in grain and straw samples were determined using RAM 281/01 as described in the analytical method section. The validated LOQ is 0.02 ppm. Concurrent method recoveries ranged from 68 to 117% for two control samples each of grain and straw fortified with tralkoxydim at 0.025 ppm. Tralkoxydim residues were undetectable in a treated samples tested (three grain and three straw samples).

In 1995, a total of 12 barley field trials were conducted in California, Colorado, Idaho, Minnesota, Montana, North Dakota, Nebraska, New York, Oregon, South Dakota and Wyoming. In eleven of these trials, a single control sample and duplicate treated samples of barley hay, grain and straw were collected. Hay samples were cut 26–43 days postapplication and were dried for an additional 3–7 days prior to sampling. Grain and straw samples were harvested 49–85 days post-treatment. Straw samples were not collected from the trial in Idaho. In the 12th trial (California), which was used as a residue decline study, single treated samples of hay, grain and straw were harvested at four post-treatment intervals. Hay samples were cut 22, 28, 36 and 41 days post-treatment and were dried for an additional 6–11 days prior to sampling. Grain and straw samples were harvested at 82, 89, 96 and 103 days post-treatment. Samples were held in frozen storage for a total of 230–380 days in <-18°C conditions prior to analysis. Residues of tralkoxydim in hay, straw and grain were determined using a LS/MS-MS method. Concurrent method recoveries of tralkoxydim were 70–88% from two control samples fortified at 0.02 ppm (method LOQ). Tralkoxydim residues were <0.02 ppm in/on all treated samples of hay, forage and grain.

Rye and Triticale

There are no rye and triticale field trial studies on file. However, based on wheat and barley field trial data, it can be concluded that tralkoxydim residues will not occur at significant amounts in cereals, when treated and harvested according the label directions. Potential residue that may occur in rye and triticale are subsequently covered under the general MRL at 0.1 ppm (subsection B.15.002(1) of the *Food and Drug Act*). Additional field trials for rye and triticale are required to establish MRLs for these commodities.

1.3.3 Livestock Residues

Tralkoxydim residues are expected to occur in very low amounts in animal matrices; therefore, studies depicting the magnitude of residues in livestock are not required.

1.3.4 Confined Crop Rotation

An adequate confined crop rotation study was submitted to the PMRA. A previous USEPA review of the study is considered to be acceptable by the PMRA and is provided below. Based on data from the study, it can be concluded that no additional plant back intervals are required.

Uptake of ^{14}C-Tralkoxydim Residues into Rotational Crops (Evans JDHL, et al., 1995, PMRA #1581327)

^{14}C-phenyl and cyclo-hexene labeled tralkoxydim was applied to two separate uncropped plots containing sandy loam soil. Wheat and all other plant material were removed from the plots two ays prior to application. The application rate ranged from 370 to 392 g a.i./ha (1.8–1.9 imeslabel rate). Crop samples were planted in the soil after fallow periods of 30, 100 and 300 days. Four crop types were tested including leafy vegetables (spinach/mustard), grains (millet/wheat), root vegetables (turnip) and legume vegetables (soybean). The crops were

harvested at normal maturity and stored at <-10°C conditions for up to 10 months prior to analysis. Radioactivity was determined using LSC. Tralkoxydim equivalent residues in all samples were <0.01 ppm with the exceptions of straw from millet (0.001–0.045 ppm), straw from wheat (0.003–0.074 ppm), and the stems and hulls from soybeans (0.006–0.13 ppm). A summary of the residue data can be found in Table 6. The wheat straw samples were subject to extraction and further analysis. The metabolites identified were the same as those noted in the wheat metabolism studies.

Table 6 Residues in Rotation Crops After Treatment of Soil with ^{14}C-Tralkoxydim

Crop	Rotational Interval (Days)		Crop Fraction	PHI (Days)	Storage Interval (Months)[1]	Total Radioactive Residue (ppm)[2]	
	Cyclo-Hexyl Ring	Phenyl				Cyclo-Hexyl Ring	Pheayl Ring
Spinach	31	32	leaf/stem	117	8	0.007	0.009
Mustard	105	106	leaf/stem	84	10	0.008	0.003
Spinach	299	300	leaf/stem	55	5	0.008	0.003
Millet	31	32	forage	93	9	0.003	0.002
			grain	137	8	0.005	0.003
			straw			0.045	0.001
Wheat	105	106	forage	157	7	0.007	0.004
			grain	215	5	0.003	0.003
			straw			0.042	0.015
	299	300	forage	82	4	0.017	0.005
			grain	97	5	0.004	0.003
			straw			0.074	0.017
Turnip	31	32	foliage	81	9	0.02	0.006
			roots			0.005	0.003
	105	106	foliage	91	9	0.007	0.002
			roots			0.001	0.001

Crop	Rotational Interval (Days)		Crop Fraction	PHI (Days)	Storage Interval (Months)[1]	Total Radioactive Residue (ppm)[2]	
	Cyclo-Hexyl Ring	Phenyl				Cyclo-Hexyl Ring	Phenyl Ring
	299	300	foliage	77	5	0.005	0.002
			root			0.001	0.001
Soybean	31	32	bean	130	9	0.029	0.009
			stems/hulls			0.129	0.025
	105	106	pea	173	6	0.006	0.009
			stems/hulls			0.018	0.021
	299	300	bean	162	2	0.013	0.006
			stems/hulls			0.06	0.017

From USEPA review, 1998. Application rate = 370–392 g a.i./ha (1.8–1.9 times label rate).

[1] Period of sample storage (frozen in less than -10°C freezer) from harvest to analysis.

[2] Calculated as tralkoxydim equivalents.

1.3.5 Processed Food/Feed Data

A process wheat study was available on file with the PMRA along with a USEPA review of a processed barley study. Based on data from these studies, it can be concluded that no additional processing factors are required.

Achieve® Processing Study for Residues of Tralkoxydim in Wheat and Processed Wheat Commodities (Meyers TJ, 1994. PMRA # 1581328)

Wheat samples were collected, processed, and analyzed from a field trial conducted in Minnesota during the 1993 growing season. In the trial, two plots of spring wheat were treated with tralkoxydim at a rate of 280 (1.4 times label rate) and 840 g a.i./ha (4.2 times label rate). Only samples from the high treatment field were used for analysis. The PHI was 74 days. Grain samples were processed into bran, middling, shorts, flour and dust. Samples were stored frozen for up to six months prior to analysis. Wheat grain and processed commodity samples were analysed for tralkoxydim residues using method "TMJ323J", as described in the analytical method section. Sufficient recovery data (70–120%) was obtained for control samples fortified with tralkoxydim at 0.02 ppm and 0.2 ppm. Residues were non-detectable (method LOQ <0.02 ppm) in any of the grain and processed samples.

Barley Processing Study (USEPA review, 1998)

The USEPA has a review of a barley processing study. The PMRA does not have this study on file and requests the registrant to submit this study. A summary of the United States review is provided below.

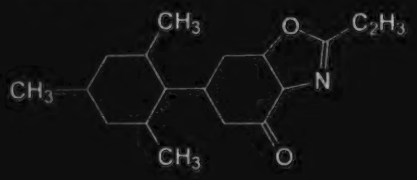
Two trials were conducted during 1994 in Idaho and Minnesota. At each site, tralkoxydim was applied to two plots of barley at a rate of 280 (1.4 times label rate) and 840 g a.i./ha (4.2 times label rate). Samples of barley grain were harvested at normal maturity at 69 and 63 days postapplication in the Idaho and Minnesota trials, respectively. Only samples from the high treatment plot in the Idaho trial underwent processing. The samples were stored for 12–23 days prior to processing into hulls, bran, flour, and pearled barley. Total storage time from harvest to analysis for all samples was within 12 months. Residues of tralkoxydim in barley grain and all processed commodities were determined using the method RAM 281/01 as described in the analytical method section. For validation, two control samples of barley grain and bran were fortified with tralkoxydim at 0.025 ppm. The recovery from these fortified samples ranged between 95 and 111%. Tralkoxydim residues were non-detectable (method LOQ <0.02 ppm) in any of the treated grain and processed samples.

Appendix VII Environmental Fate of Tralkoxydim and Its Transformation Products

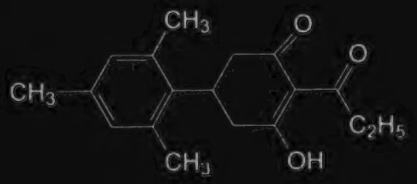
Study Type	Test Material	Study Conditions	Value or Endpoint	Interpretation	Major Transformation Products	Reference
Abiotic transformation						
Hydrolysis	Tralkoxydim	28 days, 25°C pH 5 pH 7 pH 9	DT_{50}: 6.2 days 114 days 1594 days	Not a major route of transformation at neutral and basic conditions	Compound 3	1541555
Phototransformation soil	Tralkoxydim	Sandy clay soil, pH 6.0	DT_{50}: pH 6.0, 1.4 days	Important route of transformation, hydrolysis may have contributed	Compound 3	1541555
Phototransformation water	Tralkoxydim	pH 9	DT_{50}: 2.8–6.2 days	Not a major route of transformation at neutral and basic conditions	Compound 2 and 6	1567192
		pH 4 pH 7 pH 9	DT_{50}: 0.8 days 15 days 13 days		Not determined.	1541555
Biotransformation						
Soil - aerobic	Tralkoxydim	180 days, 20°C: sancy clay loam (pH 6.5, % OM 4.7) sancy loam (pH 5.7, % CM 2.1)	DT_{50}: 3–6 days 1.1 days	Non persistent	Compound 8	1641555
		94 days, 20°C: sancy clay loam (pH 6.9, % OM 4.7) sancy loam (pH 6.7, % CM 1.1) sancy loam (pH 7.9, % CM 1.8)	DT_{50}: 2.2 days 2.5 days 5.7 days	Non persistent	Compound 8 and 17. DT_{50} determined to be 7 days for Compound 8 (soil pH 6.7) and 23–25 days for Compound 17 (soil pH 6.9–7.9)	1567194
Soil–anaerobic	Not available					
Water/sediment–aerobic	Tralkoxydim	Two systems: 135 days, 20°C, pH 8	DT_{50}: 34–82 days water; 51–154 days whole system	Moderately persistent. Tralkoxydim predominantly found in the water column.	Compound 6; the majority was found in sediment extracts.	1567195

Study Type	Test Material	Study Conditions	Value or Endpoint	Interpretation	Major Transformation Products	Reference
	Tralkoxydim	Two systems: 119 days; 20 °C; pH 7.6–7.7	DT_{50}: 5–>119 days whole system	Non persistent to moderately persistent. No significant accumulation in the sediment	Compound 3 and 8	1541555
Water/sediment–anaerobic			DT_{50}: 88–204 days water; 91–204 days whole system	Moderately persistent to persistent	Compound 6	
Residue trials	Tralkoxydim		DT_{50} = 1.2	Non persistent	Not determined	1576393
Mobility						
Adsorption/ desorption	Tralkoxydim	Six soils: 20 °C; pH 5.3–8.0; % OM 1.1–13.1	K_d 0.1–6.5 K_{OC} 1–1025	Moderately to very high mobility	Not determined	1641555
		Four soils: 20°C; pH 5.4–6.8; % OC 0.5–3.1	K_d 1.2–1.7 K_{OC} 34–340			
		Two soils: 20°C; pH 6.2–6.8; % OM 0.5–3.7	K_d 0.2–2.2 K_{OC} 51–100			1567196
	Compound 17	Six soils: 20°C; 5.7–8.4; % OM 1.0–5.1	K_d 0.04–3.7 K_{OC} 2–200	Moderately to very high mobility		1567197
	Compound 8	Six soils: 20°C; 5.7–8.5; % OM 1.0–5.1	K_d 0.07–2.1 K_{OC} 2–359	Moderately to very high mobility		1567198
Soil column leaching	Tralkoxydim	Two soils: 20°C, no other information	4 to 7% of the applied radioactivity was detected in the leachate		Transformation products could not be identified; no single product represented more than 0.7% of the applied radioactivity.	1641555
Field studies						
Field dissipation	Tralkoxydim	Three Canadian sites: two in Saskatchewan and one in Manitoba. Four United States sites: North Dakota, Illinois, Washington and Montana.	DT_{50}: 1.6 to 2.2 days DT_{90}: 1–4 days Non persistent. No detection of residues below 10 cm soil depth beyond 30 days.		No information available regarding the leaching potential of major transformation products under field conditions.	1641555

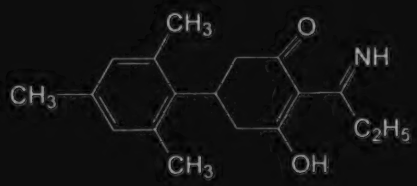
Appendix VIII Major Transformation Products of Tralkoxydim



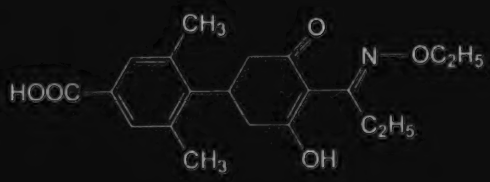
Compound 3
3-ethyl-4,5,6,7-tetrahydro-4-oxo-6-(2,4,6-trimethylphenyl)-1,3-benzoxazole



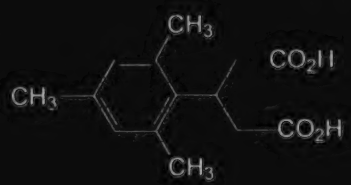
Compound 2
3-hydroxy-2-propoinyl-5-(2,4,6-trimethylphenyl) cyclohex-2-eone



Compound 6
3-hydroxy-2-(1-iminopropyl)-5-(2,4,6-trimethylphenyl)cyclohex-2-enone



Compound 8
4-(2-[1-(ethoxyimino)propyl]-3-hydroxy-2-cyclohexen-1-one-5-yl)-3,5-dimethylbenzoic acid (tralkoxydim acid)



Compound 17
3-(2,4,6-trimethylphenyl)pentanedioic acid

Appendix IX Environmental Toxicity of Tralkoxydim and Its Transformation Products

Organism	Study Type	Species	Test material	Endpoint	Value (effect)	Effect of Concern	Reference
Terrestrial Species							
Invertebrate	Acute oral	Honey bee (*Apis mellifera*)	Formulation (10.1%–'JF 9517')	48-hour LD_{50}	49.9 µg a.i./bee	mortality	1641555
	Acute contact		Technical		>100 µg a.i./bee		
			Formulation (10.1%–'JF 9517')		>50 µg a.i./bee		
	Acute contact	Earthworm (*Eisenia foetida*)	Technical	14-day LC_{50} 14 d NOEC	> 1000 mg a.i./kg soil 1000 mg a.i./kg soil	mortality	1567200
				14-day LC_{50} 14 day NOEC	72 mg a.i./kg soil 32 mg a.i./kg soil		1641555
			Compound 8	14-day LC_{50} 14 day NOEC	> 1000 mg a.i./kg soil 1000 mg a.i./kg soil		1567203
			Compound 17	14-day LC_{50} 14 day NOEC	> 1000 mg a.i./kg soil 1000 mg a.i./kg soil		1567205
		Ground beetle (*Pterostichus cupreus*)	Formulation (10.1%–'JF 9517')	6-day LC_{50} 6-day NOEC	>1750 g a.i./ha 1750 g a.i./ha	mortality	1641555
		Parasitic wasp (*Aphidius rhopalosiphi*)		6-day LC_{50} 6-day NOEC	>350 g a.i./ha 350 g a.i./ha		
Birds	Acute oral	Red legged partridge (*Alectoris rufa*)	Technical	LD_{50}	>3020 / 2024 mg a.i./kg diet (♂/♀)	Mortality	1641555
		Mallard duck (*Anas platyrhynchos*)		LD_{50} NOEC	>3020 mg a.i./kg diet 3020 mg a.i./kg diet		

Organism	Study Type	Species	Test material	Endpoint	Value (effect)	Effect of Concern	Reference
	Acute dietary	Bobwhite quail (*Colinus virginianus*)		9-day LD_{50}	6237 mg a.i./kg diet		
		Mallard duck (*Anas platyrhynchos*)		8-day LD_{50} NOEC	>7400 mg a.i./kg diet 7400 mg a.i./kg diet		
	Reproduction	Bobwhite quail (*Colinus virginianus*)	Technical	NOEC	150 mg a.i./kg diet	Reproduction	1667599
		Mallard duck (*Anas platyrhynchos*)		NOEC	150 mg a.i. /kg diet		1667597
Mammals	Acute	Mice	Technical	LD_{50}	1231 / 1100 mg a.i./kg bw (♂/♀)	Mortality	
		Rat			1258 / 934 mg a.i./kg bw (♂/♀)		
	Dietary	Mice	Technical	NOAEL	37.5 mg a.i./kg/day (250 mg a.i./kg diet)	decreased body weight and body-weight gain	
	Reproduction (3-generation)	Rat	Technical	Parental/ Reproductive NOAEL	10 mg a.i./kg bw/day (1000 mg a.i. /kg diet)	reduced body-weight gain in Fo and decreased birth body weight in F_1, F_2 and F_3	
				Offspring NOAEL	10 mg a.i./kg bw/day (1000 mg a.i./kg diet)	decreased litter weight and decreased pup weight gain (F_1, F_2 and F_3)	
	4-day dietary	Deer mice (*Peromyscus monticulatus*), meadow voles (*Microtus pennsylvanicus*) and the white-footed mouse (*Peromyscus leucopus*)		NOAEL	100 mg a.i./kg bw	increased hepatic porphyrin accumulation	1641555

Organism	Study Type	Species	Test material	Endpoint	Value (effect)	Effect of Concern	Reference
Plants	Seedling emergence	10 plant species: soybean (*Glycine max*), sugar beat (*Beta vulgaris*), oilseed rape (*Brassica rapus*), teaweed (*Sida Spinosa*), velvet-leaf (*Abutilon theophrasti*), white mustard (*Sinapis alba*), maize (*Zea mays*), winter wheat (*Triticum arvense*), wild oat (*Avena fatua*) and purple nutsedge (*Cyperus rotunda*)	Formulation ("GFU519")	EC_{25} NOEC	53–>350 g a.i./ha 117–350 g a.i./ha	number of seedlings emerged seedling dry weight	1641555
	Post emergence			EC_{25} NOEC	2.76–>350 g a.i./ha 0.56–350 g a.i./ha	% visual damage reduced dry weight	
	Seedling emergence	10 plant species: corn (*Zea may)*; oat (*Avena sativa)*; onion (*Allium cepa)*; perennial ryegrass (*Lollium perenne;)*cabbage (*Brassica oleracea)*; cucumber (*Cucumis sativus)*; lettuce (*Lactuca sativa)*; soybean (*Glycine max)*; tomato (*Lycopersicon esculentum)*; turnip (*Brassica rapa)*	Formulation (80.2% –'Achieve 80 DG')	EC_{25} NOEC EC_{25} NOEC	>258 g a.i./ha 258 g a.i./ha 94–> 258 g a.i./ha 31–258 g a.i./ha	survival Shoot dry weight	1567226
	Vegetative vigour			EC_{25} NOEC EC_{25} NOEC EC_{25} NOEC	>83–>258 g a.i./ha 28–258 g a.i./ha 5–>258 g a.i./ha 3–258 g a.i./ha 13–>258 g a.i./ha 3–258 g a.i./ha	survival dry weight height	
Freshwater Organisms							
Invertebrates	Acute	*Daphnia magna*	Technical	48-hour LC_{50} NOEC	>177 mg a.i./L 47 mg a.i./L	immobility	1641555
			formulation (10% EP mixed with 'Agral 90' wetting agent)	48-hour LC_{50}	2.72 mg a.i./L		

Organism	Study Type	Species	Test material	Endpoint	Value (effect)	Effect of Concern	Reference
			formulation (25%)	48-hour LC_{50} NOEC	163 mg a.i./L 94.8 mg a.i./L		
			Compound 17	48-hour LC_{50} NOEC	85 mg a.i./L 60 mg a.i./L		1567207
			Compound 8	48-hour LC_{50} NOEC	>120 mg a.i./L 120 mg a.i./L		1567209
	Chronic	*Daphnia magna*	Technical	21-day LC_{50} (survival) NOEC (reproductive effects)	> 8.1 mg a.i./L 2.1 mg a.i./L	mortality decreased adult daphnia length	1076031
Sediment dwelling invertebrate	Chronic	*Chironomus riparius*	Compound 6	25-day NOEC LOEC	63 mg a.i./L >63 mg a.i./L	emergence and developmental rate	1567216
Fish	Acute	Mirror carp (*Cyprinus carpio*)	Technical	96-hour LC_{50} NOEC	>8.2 mg a.i./L 8.2 mg a.i./L	mortality	1641555
		Rainbow trout (*Oncorhynchus mykiss*)		96-hour LC_{50} NOEC	>7.2 mg a.i./L 7.2 mg a.i./L		
		Mirror carp (*Cyprinus carpio*)	Formulation (100 g a.i./L EP + 'Agral' wetting agent)	46-hour LC_{50} NOEC	12 mg formulation/L 4.6 mg formulation/L		
			Formulation (25% mixed with + 'At plus 411F' oil)	96-hour LC_{50} NOEC	68 mg a.i./L (270 mg formulation/L) 58 mg a.i./L (15 mg formulation/L)		
		Rainbow trout (*Oncorhynchus mykiss*)	Formulation (25% mixed with + 'At plus 411F' oil)	96-hour LC_{50} NOEC	25 mg a.i./L (100 mg formulation/L) 4.5 mg a.i./L (18 mg formulation/L)		

Organism	Study Type	Species	Test material	Endpoint	Value (effect)	Effect of Concern	Reference
		Rainbow trout (*Oncorhynchus mykiss*)	Compound 17	96-hour LC_{50} NOEC	>120 mg a.i./L 120 mg a.i./L	mortality	1567218
		Fathead minnow (*Pimephales promelas*)	Compound 8	96-hour LC_{50} NOEC	44 mg a.i./L 41 mg a.i./L		1567220
Algae	Acute	Green algae (*Selenastrum capricornutum*)	Technical	96-hour EC_{50} NOEC	>5.1 mg a.i./L 5.1 mg a.i./L	biomass and growth rate	1641555
		Blue-green algae (*Anabaena flos-aquae*)		120-hour EC_{50} NOEC	>180 mg a.i./L 56 mg a.i./L	cell density	1567222
				120-hour EC_{50} NOEC	>180 mg a.i./L 100 mg a.i./L	biomass	
				120-hour EC_{50} NOEC	>180 mg a.i./L 56 mg a/L	growth rate	
Vascular Plants	Acute	Duck weed (*Lemna gibba*)	Technical	14-day EC_{50} NOEC	2.6 mg a.i./L 0.58 mg a.i./L	frond number	1567229
				14-day EC_{50} NOEC	1.0 mg a.i./L 0.14 mg a.i./L	biomass	
		Duck weed (*Lemna gibba*)	Compound 17	7-day EC_{50} NOEC	110 mg a.i./L 30 mg a.i./L	frond number	1567231
				7-day EC_{50} NOEC	99 mg a.i./L 60 mg a.i./L	biomass	

Organism	Study Type	Species	Test material	Endpoint	Value (effect)	Effect of Concern	Reference
			Compound 8	7-dayEC_{50}	53 mg a.i./L	frond number	1567233
				NOEC	30 mg a.i./L		
				7-day EC_{50}	78 mg a.i./L	biomass	
				NOEC	30 mg a.i./L		
				NOEC	7.5	visual observation– reduced root growth	

Appendix X Summary of Screening Level Risk Assessment of Tralkoxydim to Terrestrial Invertebrates and Plants

Organism	Exposure	Endpoint Reported	EEC	RQ*	LOC Exceeded
Honeybee	Acute contact	LD_{50} – 49.9 µg a.i./bee (55.9 kg a.i./ha)	0.2 kg a.i./ha	0.004	No
Earthworm		LD_{50} 72 mg a.i./kg soil	0.089 mg a.i./ha	0.001	No
Ground beetle		> 1750 g a.i./ha	200 g a.i./ha	>0.1	No
Wolf spider		350 g a.i.ha	200 g a.i./ha	>0.6	No
Plants	corn (*Zea mays*)	EC_{25} – 2.76 g a.i./ha	200 g a.i./ha	**72**	Yes

*Risk quotients (RQ) shown in bold exceed the level of concern (RQ > 1).

Appendix XI Refined Risk Assessment of Tralkoxydim to Terrestrial Plants

Organism	Exposure	EC_{25}	Application Method	Drift EEC* (g a.i./ha)	RQ**	LOC Exceeded
Plants	Corn (*Zea mays*)	2.76 g a.i./ha	Ground	12	**4.3**	Yes
			Aerial	46	**16.7**	Yes

* EECs takes into consideration the spray drift deposition of spray quality of ASAE medium for ground (6%) and aerial application (23%) at 1 m downwind from the site of application.

** Risk quotients shown in bold exceed the level of concern (RQ > 1).

Appendix XII Summary of Screening Level Risk assessment of Tralkoxydim to Birds and Mammals

Organism	Exposure	Endpoint* (mg a.i./kg body weight/day)	Food Guild	EDE (mg a.i./kg body weight/day)	RQ**	LOC Exceeded
Birds						
Small (20 g)	Acute Oral	202.4	insectivore	10.1	0.05	No
			granivore	1.7	<0.01	No
			frugivore	5.2	0.03	No
	Dietary	66.2	insectivore	10.1	0.15	No
			granivore	1.7	0.03	No
			frugivore	5.2	0.08	No
	Reproduction	8.5	insectivore	10.1	**1.2**	Yes
			granivore	1.7	0.2	No
			frugivore	5.2	0.6	No
Medium (100 g)	Acute Oral	202.4	insectivore	7.9	0.04	No
			granivore	1.4	<0.01	No
			frugivore	4.1	0.02	No
	Dietary	66.2	insectivore	7.9	0.12	No
			granivore	1.4	0.02	No
			frugivore	4.1	0.06	No
	Reproduction	8.5	insectivore	7.9	0.9	No
			granivore	1.4	0.2	No
			frugivore	4.1	0.5	No
Large (1000 g)	Acute	202.4	insectivore	2.3	0.01	No
			granivore	0.4	<0.01	No
			frugivore	1.2	<0.01	No
			herbivore	14.3	0.07	No
	Dietary	66.2	insectivore	2.3	0.03	No
			granivore	0.4	<0.01	No
			frugivore	1.2	0.02	No
			herbivore	14.3	0.22	No

Organism	Exposure	Endpoint* (mg a.i./kg body weight/day)	Food Guild	EDE (mg a.i./kg body weight/day)	RQ**	LOC Exceeded
	Reproduction	8.5	insectivore	2.3	0.3	No
			granivore	0.4	0.04	No
			frugivore	1.2	0.1	No
			herbivore	14.3	**1.7**	Yes
Mammals						
Small (15 g)	Acute Oral	93.4	insectivore	5.8	0.06	No
			granivore	1.0	0.01	No
			frugivore	3.0	0.03	No
	Dietary	37.5	insectivore	5.8	0.15	No
			granivore	1.0	0.03	No
			frugivore	3.0	0.08	No
	Reproduction	10	insectivore	5.8	0.58	No
			granivore	1.0	0.1	No
			frugivore	3.0	0.3	No
Medium (35 g)	Acute Oral	93.4	insectivore	5.1	0.05	No
			granivore	0.9	0.01	No
			frugivore	2.6	0.03	No
			herbivore	31.7	0.34	No
	Dietary	37.5	insectivore	5.1	0.14	No
			granivore	0.9	0.02	No
			frugivore	2.6	0.07	No
			herbivore	31.7	0.85	No
	Reproduction	10	insectivore	5.1	0.51	No
			granivore	0.9	0.09	No
			frugivore	2.6	0.26	No
			herbivore	31.7	**3.2**	Yes
Large (1000 g)	Acute Oral	93.4	insectivore	2.7	0.03	No
			granivore	0.5	0.01	No

Organism	Exposure	Endpoint* (mg a.i./kg body weight/day)	Food Guild	EDE (mg a.i./kg body weight/day)	RQ**	LOC Exceeded
			frugivore	1.4	0.01	No
			herbivore	16.9	0.18	No
	Dietary	37.5	insectivore	2.7	0.07	No
			granivore	0.5	0.01	No
			frugivore	1.4	0.04	No
			herbivore	16.9	0.45	No
	Reproduction	10	insectivore	2.7	0.27	No
			granivore	0.5	0.05	No
			frugivore	1.4	0.14	No
			herbivore	16.9	**1.69**	Yes

* Acute oral and dietary endpoints that were originally expressed as a concentration (mg a.i./kg diet) have been converted to daily dose (mg a.i./kg body weight/day) and further divided by a factor of 10 in order to address differences in species sensitivity.

** Risk quotients shown in bold exceed the level of concern (RQ > 1).

Appendix XIIIA Refined Risk Assessment of Tralkoxydim to Birds

Bird Weight	Feeding Guild	Refined Exposure (mg a.i./kg bw)	RQ*	LOC Exceeded
On –field assessment				
20 g	Small insects	10.1	**1.2**	Yes
1000 g	Leaves, leafy crops	14.3	**1.7**	Yes
	Short range grass	9.7	**1.1**	Yes
	Forage crops	8.9	1.0	No
	Long grass	5.9	0.7	No
	Pods with seeds	0.6	0.07	No
Off-field assessment from ground application (6% drift deposition)				
20 g	Small insects	0.6	0.07	No
1000 g	Leaves, leafy crops	0.9	0.1	No
	Short range grass	0.5	<0.1	No
	Forage crops	0.5	<0.1	No
	Long grass	0.3	<0.1	No
	Pods with seeds	0.03	<0.01	No
Off-field assessment from aerial application (23% drift deposition)				
20 g	Small insects	2.3	0.3	No
1000 g	Leaves, leafy crops	3.3	0.4	No
	Short range grass	1.8	0.2	No
	Forage crops	1.7	0.2	No
	Long grass	1.2	0.1	No
	Pods with seeds	0.1	0.1	No

* Risk quotients shown in bold exceed the level of concern (RQ > 1).

Appendix XIIIB Refined Risk Assessment of Tralkoxydim to Mammals

Mammal Weight	Herbivore Feeding Guild	Refined Exposure (mg a.i./kg bw)	RQ*	LOC Exceeded
On –field assessment				
35 g	Leaves, leafy crops	31.7	**3.2**	Yes
	Short range grass	18.2	**1.8**	Yes
	Forage crops	16.6	**1.7**	Yes
	Long grass	11.1	**1.1**	Yes
	Pods with seeds	1.1	0.1	No
1000 g	Leaves, leafy crops	16.9	**1.7**	Yes
	Short range grass	9.7	1.0	No
	Forage crops	8.9	0.9	No
	Long grass	5.9	0.6	No
	Pods with seeds	0.6	0.1	No
Off-field assessment from ground application (6% drift deposition)				
35 g	Leaves, leafy crops	1.9	0.2	No
	Short range grass	1.1	0.1	No
	Forage crops	1	0.1	No
	Long grass	0.7	<0.1	No
	Pods with seeds	0.06	<0.01	No
1000 g	Leaves, leafy crops	1	0.1	No
	Short range grass	0.6	<0.1	No
	Forage crops	0.5	<0.1	No
	Long grass	0.4	<0.1	No
	Pods with seeds	0.03	<0.01	No
Off-field assessment from aerial application (23% drift deposition)				
35 g	Leaves, leafy crops	7.3	0.7	No
	Short range grass	4.2	0.4	No
	Forage crops	3.8	0.4	No
	Long grass	2.5	0.3	No
	Pods with seeds	0.2	<0.1	No

Mammal Weight	Herbivore Feeding Guild	Refined Exposure (mg a.i./kg bw)	RQ*	LOC Exceeded
1000 g	Leaves, leafy crops	3.9	0.4	No
	Short range grass	2.2	0.2	No
	Forage crops	2	0.2	No
	Long grass	1.4	0.1	No
	Pods with seeds	0.1	0.01	No

* Risk quotients shown in bold exceed the level of concern (RQ > 1).

Appendix XIV Summary of Screening Level Risk Assessment of Tralkoxydim to Aquatic Organisms

Organism	Exposure	Species	Endpoint Reported (mg a.i./L)	Endpoint for RA* (mg a.i./L)	EEC** (mg a.i./L)	RQ	LOC exceeded
Invertebrate	Acute	*D. magna*	LC_{50} = 2.72	1.36	0.025	0.02	No
	Chronic	*D. magna*	NOEC = 2.1	2.1	0.025	0.01	No
Fish	Acute	Rainbow trout	LC_{50}>7.2	>0.72	0.025	<0.03	No
Freshwater algae	Acute	*Selenastrum capricornitum*	96-hour EC_{50} > 5.1	>2.55	0.025	<0.01	No
Vascular plant	Acute	*Lemna gibba*	14-day EC_{50} – 1.0	0.5	0.025	0.05	No
Amphibian	Acute	Rainbow trout (surrogate)	96-hour LC_{50} > 7.2	>0.72	0.133	<0.18	No

* Endpoints used in the acute exposure risk assessment (RA) are derived by dividing the EC_{50} or LC_{50} from the appropriate laboratory study by a factor of two (2) for aquatic invertebrates and plants, and by a factor of ten (10) for fish and amphibians.

** EEC based on a 15 cm water body depth for amphibians and an 80 cm water depth for all other aquatic organisms.

Appendix XV Summary of Screening Level Risk Assessment of Tralkoxydim Transformation Products to Aquatic Organisms

Organism	Exposure	Species	Endpoint Reported (mg a.i./L)	Endpoint for RA* (mg a.i./L)	EEC** (mg a.i./L)	RQ***	Loc Exceeded
Compound 8							
Invertebrate	Acute	*D. magna*	48-hour LC_{50}>120	>60	0.0248	<0.001	No
Fish	Acute	Fathead minnow	96-hour LC_{50} = 44	4.4	0.0248	<0.01	No
Amphibians	Acute	Fathead minnow (surrogate)	96-hour LC_{50} = 44	4.4	0.132	0.03	No
Vascular plant	Acute	*Lemna gibba*	LC_{50} = 53	26.5	0.0248	<0.001	No
Compound 17							
Invertebrate	Acute	*D. magna*	48-hour EC_{50} = 85	42.5	0.019	<0.0001	No
Fish	Acute	Rainbow trout	96-hour LC_{50} > 120	>12	0.019	<0.01	No
Amphibians	Acute	Rainbow trout (surrogate)	96-hour LC_{50} > 120	>12	0.101	<0.01	No
Vascular plant	Acute	*Lemna gibba*	LC_{50} = 99	49.5	0.019	<0.001	No
Compound 6							
Invertebrate	Chronic	*Chironomus riparius*	NOEC = 63	63	0.0217	<0.001	No

* Endpoints used in the acute exposure risk assessment (RA) are derived by dividing the EC_{50} or LC_{50} from the appropriate laboratory study by a factor of two (2) for aquatic invertebrates and plants, and by a factor of ten (10) for fish and amphibians.

** EEC based on a 15 cm water body depth for amphibians and a 80 cm water depth for all other aquatic organisms. EECs for transformation products were determined by assuming 100% conversion of tralkoxydim to the transformation products and correcting for molecular weight.

*** Risk quotients shown in bold exceed the level of concern (RQ > 1).

Appendix XVI Monitoring Data

Water Monitoring Data

A search for tralkoxydim water monitoring data in Canada resulted in limited information being available. A request was sent to the Federal Provincial and Territorial representatives from all of the provinces and territories in Canada requesting water monitoring data for tralkoxydim along with other active ingredients currently under re-evaluation. Any data received as a result of this request will be considered and the information contained here will be updated, if necessary.

One dataset in the PMRA database contained data for tralkoxydim. This dataset contained data on various pesticide concentrations, including tralkoxydim in Haynes Creek Watershed in Alberta from spring 1995 to fall 1996 (PMRA # 1307584). Tralkoxydim was not detected on any of the three cultivated fields in the area (detection limit 0.02 µg/L).

The United States databases were searched for detections of tralkoxydim. All the databases searched (the United States Geological Survey National Water Quality Assessment program (NAWQA), National Contaminant Occurance Database (NCOD) and the USEPA STORET database) did not contain information on tralkoxydim. The NAWQA program does not have tralkoxydim on the analyte list and no information was submitted to STORET and NCOD for tralkoxydim.

The absence of monitoring data in both Canada (except one dataset from Alberta) and the United States did not allow for an estimation of the residues of tralkoxydim, in potential drinking water sources, to be calculated through statistical analysis of monitoring data. The drinking water values available for use in the exposure risk assessment were those determined by the Level 1 water models.

Appendix XVII Label Amendments for Commercial Class Products Containing Tralkoxydim

A) Label Changes Relating to Human Health

GENERAL LIMITATIONS

PRECAUTIONARY STATEMENTS

PROTECTIVE CLOTHING AND EQUIPMENT:

- Workers must wear coveralls over long-sleeved shirt, long pants and chemical resistant gloves when mixing, loading and during clean up or when adjusting or repairing the sprayer.
- Applicators must wear long-sleeved shirt and long pants.

RESTRICTED-ENTRY INTERVAL:

- For all uses, **DO NOT** enter or allow worker entry into treated areas during the restricted-entry interval (REI) of 12 hours.

DIRECTIONS OF USE

- Only one application per season is permitted.

- Apply only when the potential for drift to areas of human habitation or areas of human activity such as houses, cottages, schools and recreational areas is minimal. Take into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings.

B) Label Changes Relating to Environment

Add to **ENVIRONMENTAL HAZARDS**:

> **TOXIC** to non target terrestrial plants. Observe buffer zones specified under **DIRECTIONS FOR USE**.

The following is required as a standard label statement for runoff:

> To reduce runoff from treated areas into aquatic habitats avoid application to areas with a moderate to steep slope, compacted soil or clay.
>
> Avoid application when heavy rain is forecast.

Contamination of aquatic areas as a result of runoff may be reduced by including a vegetative strip between the treated area and the edge of the water body.

Add to **DIRECTIONS FOR USE**:

Field sprayer application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE) medium classification. Boom height must be 60 cm or less above the crop or ground.

Aerial application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply when wind speed is greater than 16 km/h at flying height at the site of application. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE) medium classification. To reduce drift caused by turbulent wingtip vortices, the nozzle distribution along the spray boom length **MUST NOT** exceed 65% of the wing or rotorspan.

Buffer Zones:

The buffer zones specified in the table below are required between the point of direct application and the closest downwind edge of sensitive terrestrial habitats (such as grasslands, forested areas, shelter belts, woodlots, hedgerows, riparian areas and shrublands).

Method of Application	Buffer Zones (metres) Required for the Protection of:
	Terrestrial Habitat
Field Sprayer*	3
Aerial (fixed-wing)	100
Aerial (rotary-wing)	80

* For field sprayer application, buffer zones can be reduced with the use of drift reducing spray shields. When using a spray boom fitted with a full shield (shroud, curtain) that extends to the crop canopy, the labelled buffer zone can be reduced by 70%. When using a spray boom where individual nozzles are fitted with cone-shaped shields that are no more than 30 cm above the crop canopy, the labelled buffer zone can be reduced by 30%.

When a tank mixture is used, consult the labels of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture.

References

A) Studies/Information Provided by the Applicant/Registrant

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1223689	1986, ACUTE ORAL TOXICITY TO THE RABBIT., DACO: 4.2.1
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1223683	1988, TRALKOXYDIM: 2 YEAR FEEDING STUDY IN THE RAT, DACO: 4.4.1
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